2024

National Center for Toxicological Research

Annual Report

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

FDA U.S. FOOD & DRUG ADMINISTRATION

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INTRODUCTION & DIRECTOR MESSAGE

The National Center for Toxicological Research (NCTR), located in Jefferson, Arkansas, was established in 1971 as a national resource to conduct integrated toxicological research and foster interagency, academic, and industrial collaboration in support of risk-assessment needs related to public health.

The one-million square foot research campus plays a critical role in the missions of FDA and the Department of Health and Human Services to promote and protect public health. The unique scientific expertise of NCTR in biochemical toxicology, bioinformatics and biostatistics, genetic and molecular toxicology, microbiology, neurotoxicology, and systems biology supports regulatory decision-making related to FDA-regulated products.

This 2024 calendar-year annual report showcases selected accomplishments, areas of focus, initiatives, and more.

FDA's National Center for Toxicological Research Campus, Jefferson, Arkansas

Dr. Tucker Patterson, NCTR Director

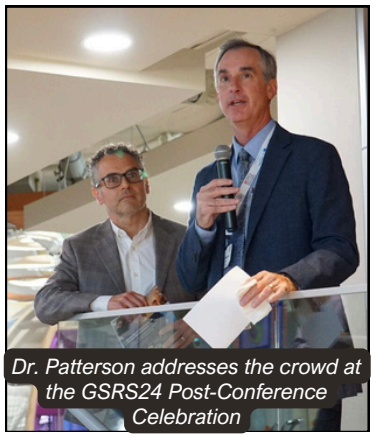
The FDA's National Center for Toxicological Research (NCTR) is a laboratory research center in the Office of the Chief Scientist that supports the FDA regulatory product centers. For over 50 years, NCTR has served to address the FDA's needs of nonbiased, high-quality science accomplished through global collaboration, state-of-the-art training, and innovative scientific-based solutions.

NCTR continues to survey current landscapes and focus on FDA needs by providing positive contributions, reliable data, and new scientific methods. NCTR sets its vision on the FDA horizon to provide positive contributions, trustworthy data, and innovative tools, all of which assist the Agency with its public health mission.

I am nearing the completion of my third year as NCTR Director and it has certainly been a privilege to serve in this capacity. The outstanding cadre of research scientists and support staff continually impress me with not only the outstanding research provided to the Agency, but also with the development of innovative science. This year was certainly no different and I know you will be just as impressed as I am with the 2024 accomplishments contained in this report.

Dr. Tucker Patterson with FDA Commissioner, Dr. Rob Califf, and Acting Chief Scientist, Dr. David Strauss

> *The outstanding cadre of research scientists and support staff continually impress me with not only the outstanding research provided to the Agency, but also with the development of innovative science.*



Dr. Patterson addresses the crowd at the GSRS24 Post-Conference Celebration

ABOUT NCTR

NCTR Mission

Address FDA's needs with high-quality research and serve as a 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.

Personnel Resources

- 5 offices
- 6 research divisions
- ~500 employees

Specialized Facilities and Physical Resources

- 1M+ sq. ft., 30 buildings
- 100+ experimental laboratories
- AAALAC-accredited animal facilities
- Bio-imaging
- Inhalation Toxicology Facility
- Nanotechnology Core Facility
- Analytical Chemistry

Major Functions

- Provide interdisciplinary toxicology research solutions and consultations that support current and anticipate future FDA needs.
- Use multidisciplinary research teams to develop novel translational research approaches that provide FDA methods to address regulatory questions.

Scientific Expertise

- Animal models including chronic bioassays
- Antimicrobial drug resistance
- Artificial intelligence and machine learning
- Computational modeling
- Developmental, reproductive, behavioral toxicology
- Genetic toxicology
- In vivo/In vitro metabolism and PBPK modeling
- MALDI Imaging Mass Spectrometry (MALDI-IMS)
- Microbiome and host interactions
- Neurochemistry, neuropathology, behavioral studies
- New Approach Methods (NAMs)
- Perinatal and maternal health
- Predictive toxicology
- Translational biomarker discovery
- Virology

ORGANIZATIONAL ABBREVIATIONS

About NCTR

To help you navigate the 2024 NCTR Annual Report, here is a helpful list of acronyms and abbreviations you may refer to while reading. You may also visit the **FDA Acronyms and Abbreviations Database**.

NCTR Division Abbreviation	NCTR Division Full Name	NCTR Office Abbreviation	NCTR Office Full Name
DBB	Division of Bioinformatics and Biostatistics	OD	Office of the Director
DBT	Division of Biochemical Toxicology	OM	Office of Management
DGMT	Division of Genetic and Molecular Toxicology	OR	Office of Research
DM	Division of Microbiology	OSC	Office of Scientific Coordination
DNT	Divison of Neurotoxicology	RCRM	Office of Regulatory Compliance and Risk Management
DSB	Division of Systems Biology		

FDA Office/Center Abbreviation	FDA Office/Center Full Name	FDA Office/Center Abbreviation	FDA Office/Center Full Name
CBER	Center for Biologics Evaluation and Research	ODT	Office of Digital Transformation
CDER	Center for Drug Evaluation and Research	OEA	Office of External Affairs
CDRH	Center for Devices and Radiological Health	OFEMSS	Office of Facilities Engineering and Mission Support Services
CTP	Center for Tobacco Products	OII	Office of Inspections and Investigations (formerly ORA)
CVM	Center for Veterinary Medicine	OMA	Office of Media Affairs
HFP	Human Foods Program (formerly CFSAN)	OWH	Office of Women's Health
OC	Office of the Commissioner	OMHHE	Office of Minority Health and Health Equity
OCS	Office of the Chief Scientist	PHCE	Perinatal Health Center of Excellence

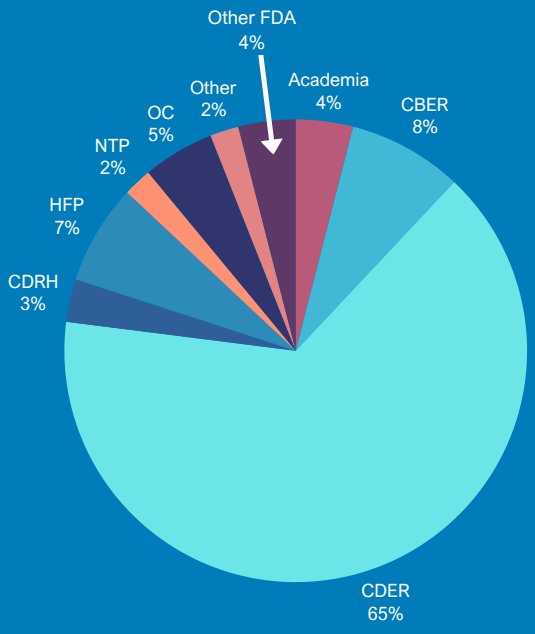
Outside Org Abbreviation	Organizations Outside FDA	Outside Org Abbreviation	Organizations Outside FDA
AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care International	NCATS	National Center for Advancing Translational Sciences
ARA	Arkansas Research Alliance	NTP	National Toxicology Program
AR-BIC	Arkansas Bioinformatics Consortium	OECD	Organization of Economic Cooperation and Development
CDC	Centers for Disease Control and Prevention	ORISE	Oak Ridge Institute for Science and Education
EPA	Environmental Protection Agency	UAMS	University of Arkansas for Medical Sciences
HESI/GTTC	Health and Environmental Sciences Instititute/Genetic Toxicology Technical Committee	USDA	United States Department of Agriculture

NCTR Research Protocol Activity

	2022	2023	2024
Publications	139	120	122
Technical Reports	39	59	42
New Protocols	47	41	44

Percentage of total active protocols by collaborator, as of November 2024

90% of NCTR Active Protocols are with Research Collaborators



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 key research projects and other related metrics that are tracked and published in FDA-TRACK, such as GovDelivery subscriptions, research publication measures, and key projects.

Sign up for NCTR mailing lists.

OUTREACH

NCTR staff attended and presented at numerous conferences and seminars internal and external to FDA in 2024.

AR-BIC 2024

The theme for the Arkansas Bioinformatics Consortium (AR-BIC) 2024 conference was "Real World Impact of Artificial Intelligence (AI)." The two-day event featured several high-profile guest speakers and moderators, including FDA's Chief Scientist and Principal Deputy Commissioner, Dr. Namandjé Bumpus, and Dr. Rich Woychick, Director of the National Institute of Environmental Health Sciences (NIEHS). NCTR Center Director, Dr. Tucker Patterson facilitated a roundtable discussion on AI with Drs. Bumpus and Woychick. Two of NCTR's postdoctoral fellows were named winners in the poster contest which recognizes research contributions from students.

Read the Research Highlight showing NCTR's contributions to AR-BIC.

Antimicrobial Agents in Veterinary Medicine

Delegates from NCTR attended the Twelfth International Conference on Antimicrobial Agents in Veterinary Medicine (AAVM), held in Athens, Greece, June 16-19, 2024. Researchers from NCTR's Division of Microbiology, attendees from FDA's Center for Veterinary Medicine, and stakeholders from South America and Europe participated in an exchange of scientific ideas.

Read the Research Highlight for NCTR's participation in AAVM.

FDA Grand Rounds

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

In 2024, two Grand Rounds sessions were presented by NCTR researchers.

- *Salmonella* and *Escherichia coli*: Challenges Along the One Health Continuum (Dr. Steven Foley, DM)
- Evaluating Mutagenicity by Error-Corrected Sequencing (Dr. Javier Revollo, DGMT)

CONFERENCES AND MEETINGS

Outreach

FDA Omics Days 2024

At the FDA Omics Days 2024, the FDA Omics Working Group hosted speakers from industry, academia, and government to discuss topics important to the FDA. The in-person/virtual hybrid event on September 12 included sessions on contemporary topics in the fields of precision medicine, multi-omics, and One Health. Seven posters by NCTR researchers were presented.

Watch the event recording and view NCTR posters.

FDA Foods Program Regulatory Science Conference

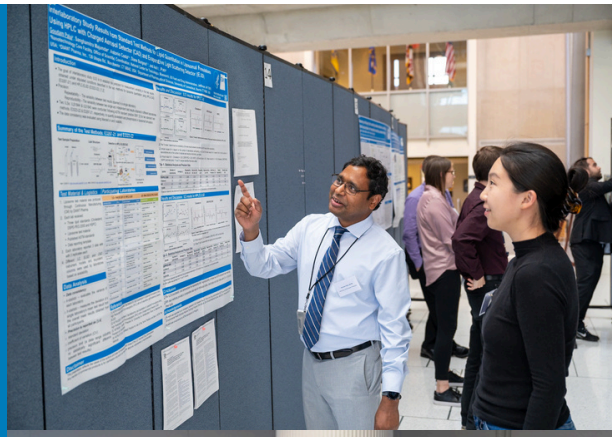
The FDA Foods Program Regulatory Science Conference (FPRSC) was held in-person September 10-11 at the FDA Center for Food Safety and Applied Nutrition (CFSAN) Campus in College Park, Maryland. The conference offered an opportunity to showcase the important, mission-relevant research being carried out across the Foods Program and provided a platform for FDA staff to share their technical expertise and network with colleagues. The conference also included poster presentations from different FDA centers, including NCTR. NCTR's contribution to FPRSC included a "State of the Science" talk by NCTR Director, Dr. Tucker Patterson, two oral presentations by NCTR staff, and nine poster presentation abstracts. In addition, Ashraf Khan, Ph.D. — Senior Biomedical Research and Biological Product Assessment Service Expert, Division of Microbiology — served on the conference committee.

FDA NanoDay Symposium 2024 (Hybrid)

The internal-to-FDA 2024 National Nanotechnology Day was held at FDA's White Oak Campus in Washington, D.C. and virtually on October 9, 2024. This event is presented annually by FDA's Nanotechnology Task Force—headed by NCTR's Dr. Anil Patri (Director, OSC Nanotechnology Core Facility)— to examine recent developments, emerging topics, and implications in the field of nanotechnology. This year's focus was on the past, present, and future of nanotechnology, which is vitally important to FDA's mission, the Oncology Center of Excellence, and FDA medical product centers.

FDA Commissioner Dr. Robert Califf provided opening remarks, and the agenda included speakers from NCTR, FDA/CBER, FDA/CDER, FDA/Human Foods Program, and the National Institutes of Health. An online poster gallery and flash talks were available during the morning session and seven NCTR posters were presented.

Read more about Nanotechnology at NCTR here.



CONFERENCES AND MEETINGS

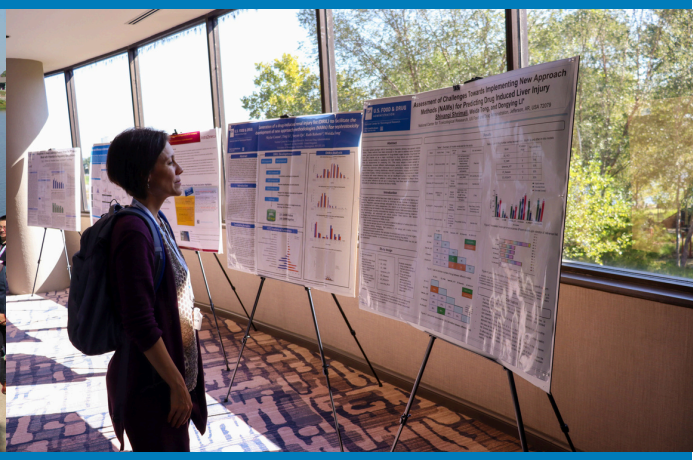
Outreach

Global Summit on Regulatory Science

The 14th Global Summit on Regulatory Science (GSRS24) was held in Little Rock, Arkansas on September 18-19, 2024, with NCTR staff providing support and coordination of the Summit. This year's conference was co-hosted by FDA and the Global Coalition for Regulatory Science Research (GCRSR), which is comprised of regulatory-science leaders from around the world. Around 200 participants attended the conference, including more than 50 international participants from 15 countries.

Pre-Conference Workshop/Collabathon

A pre-meeting workshop was held September 17. “A Dive into Digital Transformation: Navigating the FAIR Data Frontier of Regulatory Science—An EBTC Workshop” was an interactive workshop designed to elevate participants' understanding of FAIR (Findable, Accessible, Interoperable, and Reusable) data principles, with a focus on practical application in regulatory science.



GSRS Conference Days 1-2 Highlights

- Welcome Remarks by GCRSR Chair, Dr. Weida Tong (Director DBB, NCTR); NCTR Center Director, Dr. Tucker Patterson; and FDA Commissioner, Dr. Robert Califf
- An expert opinion panel on “Is Regulatory Science Ready for AI?” moderated by Dr. Weida Tong

FDA Session Co-Chairs

- Dr. Tucker Patterson, NCTR Center Director, and Dr. David Strauss, FDA Acting Chief Scientist (Plenary Session: Global Landscape of Digital Technology in Regulatory Science)
- Dr. William Slikker, Jr., Ret. NCTR Center Director (Digital Technology for Reg. Products and Public Health)
- Dr. Suzanne Fitzpatrick, Sr. Advisory for Toxicology, CFSAN (Challenges/Opportunities of AI/ML in Reg. Science)
- Dr. Dongying Li, Staff Fellow, DBB, NCTR (Generative AI for Reg. Applications)

FDA Presentations

- “AskFDALabel: Enhancing Drug Reviewers’ Experience with LLMs in Daily Missions” – Dr. Leihong Wu, Research Scientist (DBB, NCTR)
- “Digital Innovations for Drug Review at U.S. FDA” – Dr. Lilliam Rosario, Director (Office of Computational Science, Office of Translational Science, CDER)
- "Transforming the Future of Regulatory Science" – Mr. Ram Iyer, Chief Data Officer (FDA's Office of Digital Transformation)

See the full GSRS24 Program here | ***Read the Research Highlight***

CONFERENCES AND MEETINGS

Outreach

International Conference on Food Safety and the 39th Korean Society of Food Safety Annual Meeting

International Conference on Food Safety and the 39th Korean Society of Food Safety Annual Meeting was held in Jeju, South Korea, on November 20-22, 2024. NCTR sent two representatives, Dr. Steven Foley (Director, DM) and Dr. Raj Nayak (Associate Director, RCRM). Several important food safety related topics were covered at the conference, including regulatory science for emerging food technologies; strategic quality research and management approaches to foods and veterinary drugs; integrated risk assessment platforms; quality control; rapid, accurate and real time food testing; microbial hazards; antimicrobial resistance and virulence in foodborne pathogens; next generation technologies; transgenic foods; and applications of smart predictive technologies.

Dr. Steve Foley and Dr. Raj Nayak at the International Conference on Food Safety in Jeju, South Korea.

NCTR Presentations

- *Plenary Session*: "Assessment of virulence and antimicrobial resistance characteristics in *Salmonella enterica*" – Steven Foley, Ph.D.
- *Oral Presentation*: "Emerging concerns about antimicrobial resistance in foodborne pathogens: An ongoing One Health continuum paradigm" – Raj Nayak, Ph.D.
- *Oral Presentation*: "Emerging challenges: Plasmids and benchtop verification still hold a place" – Kristina Feye, Ph.D. and Steven Foley, Ph.D.

NCTR's Summer Student Research Program

NCTR's highly successful Summer Student Research Program (SSRP) is administered by the Oak Ridge Institute for Science and Education (ORISE) and is designed for science and mathematics students preparing for future careers in toxicology, regulatory science, or related scientific disciplines. The 10-week summer program provides hands-on research and laboratory experience mentored by FDA scientists.

In 2024, 18 students representing 11 states were able to intern with NCTR scientists and gave researchers the opportunity to impart their love of science and technology to students. The students also had several opportunities to submit abstracts and present their research in public forums such as:

- Central Arkansas Undergraduate Summer Research Symposium – July 24, 2024
- FDA Annual Student Scientific Research Day – August 1, 2024

Read the Research Highlight on SSRP.

CONFERENCES AND MEETINGS

Outreach

Society of Toxicology

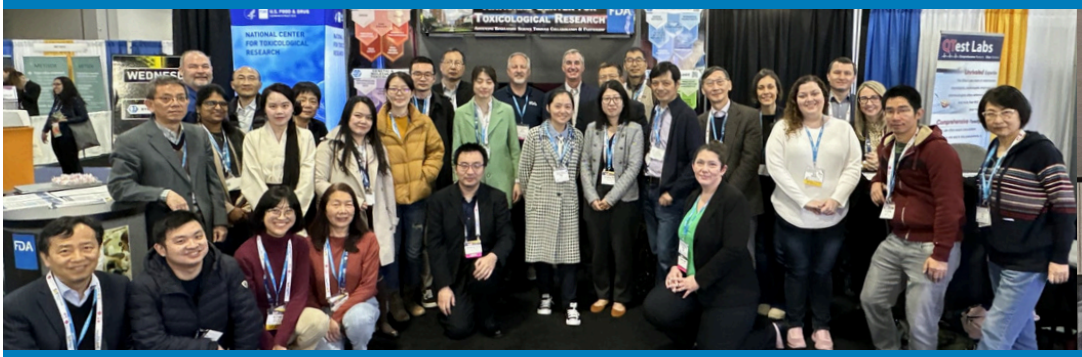
63rd Annual Meeting and ToxExpo

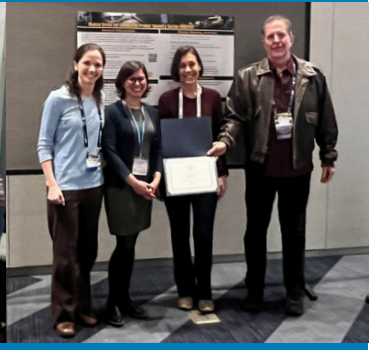
NCTR researchers and administrative professionals had the opportunity to attend the Society of Toxicology 63rd Annual Meeting and ToxExpo in Salt Lake City, Utah, March 10-14, 2024. This highly anticipated meeting brought together over 5,000 toxicologists and professionals featuring 69 scientific sessions and an impressive showcase of over 2,000 poster presentations. ***View list of 46 NCTR presentations***.

Participants also had the opportunity to visit the three-day ToxExpo which featured more than 250 booths representing industry, academia, and government organizations, including NCTR's booth. Visitors learned about training and job opportunities at NCTR and about research we are conducting.

SOT Awards by NCTR Staff

- ***Biological Modeling Specialty Section Best Trainee Abstract Finalist Award*** — "Development of a BERT-Based Language Model for Extracting Adverse Events from Social Media Data" (Dr. Fan Dong, DBB)
- ***Best Poster Award, SOT Medical Device and Combination Product Specialty Section*** "Evaluation of the Ability of the In Vitro Reconstructed Human Epidermis (RhE) Irritation Assay to Predict the Irritation Potential of Medical Devices Compared with the In Vivo Intracutaneous Reactivity Assay per ISO 10993-2" (DBT researchers: Camila Silva, Tetyana Kudlyk, Nathan Twaddle, and Luísa Camacho)





SOT-FDA Colloquium on Emerging Toxicological Science

DBT Deputy Director, Dr. Luísa Camacho, and Dr. Barbara Kaplan of Mississippi State University, co-chaired the SOT-FDA Colloquium on Emerging Toxicological Science on the "Current State of the Science: Toxicology of Cannabidiol and Other Cannabinoids." The colloquium, held online on May 8, 2024, had over 400 attendees from 25 countries. Topics covered included cannabidiol (CBD) in the context of the cannabinoids landscape, the current knowledge on CBD's pharmacokinetics, areas of action, and potential targets of toxicity, as well as potential exposures and biological activities of other minor cannabinoids. A recording of the presentations and follow-up roundtable discussion can be accessed here.

South Central Chapter of the Society of Toxicology Fall Meeting

Several NCTR researchers participated in the South Central Chapter of SOT Fall Meeting on Friday, December 6, 2024, at the UAMS Campus. Dr. Tucker Patterson (NCTR Center Director) and Dr. Luísa Camacho (DBT Deputy Director) participated in a Careers in Toxicology Panel Discussion. Dr. Seyed Mohamad Sadegh Modaresi (DBT) and Dr. David N. King'uyu (DNT) also participated in the postdoctoral platform presentation competition. The meeting focused on current research and opportunities in toxicology and featured poster sessions, scientific platform presentations, and keynote presentations by distinguished researchers and career experts.

STAFF WHO GIVE BACK

Outreach

Staff at the Jefferson Labs campus demonstrated their love for fellow humanity by giving of their time, money, and service!

Arkansas Food Bank

Making an Impact: NCTR Employees Work Together to Combat Food Insecurities in Arkansas

After volunteering at the Arkansas Food Bank with other NCTR staff last year, Joe Fowler, Supervisory Health Scientist (RCRM), wanted his daughters to have the experience of seeing how hard work and working together as a team can help so many people throughout the state. In July, he and his daughters volunteered one Saturday and were pleasantly surprised to see two other NCTR employees there!

Bridgett Green Knox, Biologist (DBB), has been volunteering there with her husband and sons since 2018. Anna Williams, Biologist (DSB), is a part-time Volunteer Operations Supervisor, overseeing/assisting volunteers on the bagging, boxing, packaging, delivering, etc., of the various foods donated to the food bank.

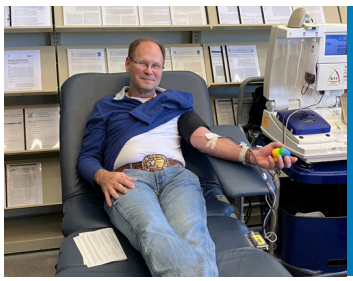
As a bonus, after signing in for our shift we noticed Bridgett Green Knox, along with her son in the waiting area. Another NCTR colleague Anna Williams (DSB) was helping out in the warehouse area. Working together, we bagged up over 9000 lbs. of potatoes for distribution to Arkansans living with food insecurity.

Jefferson Labs Staff Volunteer During the 2024 Holiday Season

Over 40,500 pounds of food were sorted and packaged by Jefferson Labs employees who signed up for volunteer slots this past holiday season at the Arkansas Foodbank. This volunteer work took place in support of the Combined Federal Campaign (CFC) on December 12 and 19, 2024.

Jefferson Labs staff sorted and prepared a total of 32 pallets, 40,552.5 pounds, and 1,185 boxes (cereal, juice, milk, canned soup, canned vegetables, and boxed meals), with each box of food weighing over 30 lbs. This equated to around 20,475 total meals for Arkansans living with food insecurity.

32	40.5K	1185	20K+
Pallets	Pounds	Boxes	Meals



Jefferson Labs Blood Drives

Twenty-one units of blood were collected from employees who accepted the Our Blood Institute challenge of “standing tall above the rest” on March 26. Blood drives were also coordinated on campus July 23 and November 26.

2024 RESEARCH THEMES

Alternative Methods

- NCTR continued prioritizing the advancement of new alternative methods (NAMs) for regulatory use by studying:
  - Human hepatotoxicity, liver toxicity, or liver injury models
  - Human cardiotoxicity models (e.g., hi-PSCs and engineered heart tissue)
  - Fertility models (e.g., spermatogenesis, folliculogenesis, placenta permeability)
  - Gastrointestinal tract models
- Another study—completed by members of the FDA Alternative Methods Working Group which includes several NCTR scientists—evaluated the potential value of animal microphysiological systems for toxicological studies. A report was published, indicating that it is a useful alternative method to animal experimentation.
- NCTR researchers continue to study opioids using neural stem cell models that can mimic or model particular developmental stages of the human brain. These models provide a means to conduct systematic dose-dependent response and time-course studies allowing rapid discovery of potential pathways of toxicity. For example, a recent study using neural stem cells exposed to fentanyl at micromolar concentrations for 24 hours revealed a role of a sphingolipid pathway in fentanyl-mediated neural cell inflammation and neurotoxicity. A manuscript describing these findings has been completed and submitted for publication. Findings from this study were also presented at ICNA 2024 and SOT 2024.

2024 NAMs Select Publications

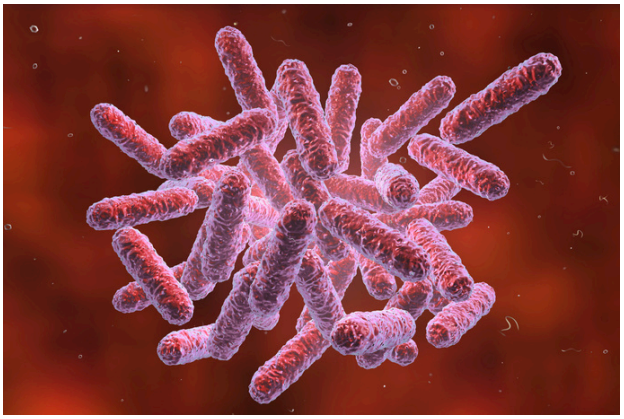
- "Repeat Treatment of Organotypic Airway Cultures with Ethyl Methanesulfonate Causes Accumulation of Somatic Cell Mutations without Expansion of Bronchial-Carcinoma-Specific Cancer Eriver Mutations." In: *Mutation Research - Genetic Toxicology and Environmental Mutagenesis*
- *"*Evaluating the Mutagenicity of *N*-nitrosodimethylamine in 2D and 3D HepaRG Cell Cultures using Error-corrected Next Generation Sequencing*."* In: *Genotoxicity and Carcinogenicity*
- "Use of Lentivirus-Based Method for Establishing TK6 Human Cell Lines Expressing Cytochrome P450 and its Applications in Genotoxicity Testing." In: *Current Protocols*
- *"*Evaluation of a Microphysiological Human Placental Barrier Model for Studying Placental Drug Transfer." In: *Reproductive Toxicology*

Antimicrobial Resistance

NCTR continues to study antimicrobial resistance (AMR) and due to its global public health threat, AMR is considered one of FDA's Focus Areas of Regulatory Science. In 2024, NCTR scientists:

- Collaborated with CVM to develop a virulence factor database, which assists FDA in its goals of addressing One Health concerns related to antimicrobial resistance and the spread of disease-causing pathogens. An article was published in *Scientific Reports*, and you can view the FDA Grand Rounds presentation on this topic here.
- Completed a study that evaluated the influences of different antimicrobial compounds on the function of efflux pumps—systems that pump the antibiotics out of the bacterial cells before they become too toxic for the bacteria, thereby limiting the effectiveness of the treatments. The results of this project helped to provide valuable scientific information on antimicrobial resistance mechanisms in enteric bacteria to help improve the safety of the human food supply (*Poultry Science*, *Frontiers in Microbiology*).
- Developed a novel polymicrobial biofilm model for studying biofilm formation in a variety of pathogens—including *Pseudomonas aeruginosa* and *Staphylococcus* species—enabling the safety assessment of medical device and bacterial interactions between different species in a biofilm complex (*Antibiotics*, *Cells*).

Read more about Antimicrobial Resistance research at NCTR here.



Computer illustration of Enterobacteriaceae bacteria

2024 RESEARCH THEMES

Artificial Intelligence & Bioinformatics

NCTR continues to use advanced artificial intelligence (AI) technologies to both compile unique FDA datasets and design software applications specific to each product center's needs. These capabilities may serve to improve public health and expedite FDA review. In 2024, NCTR scientists:

- Published a manuscript which lays out a strategy to harness the public large language models (LLMs) for FDA-sensitive data in a secure environment.
- Explored the utility of ChatGPT and other generative AI models to automate scientific literature screening, enhancing the safety of FDA-regulated drug products.
- Published the DICTrank Dataset—containing the largest number of drugs ranked by their risk of drug-induced cardiotoxicity (DICT) using FDA-approved drug labeling documents—on FDA.gov.
- Published the DIRIL Dataset—comprised of 317 single-molecule, oral administered drugs for human use, annotated for drug-induced renal injury (DIRI) and nephrotoxicity and confirmed using FDA drug labeling—on FDA.gov.

Explainable AI

In 2024, NCTR researchers achieved two significant milestones to advance Explainable AI in FDA regulatory activities:

1. Evaluated predictive modeling in biomedical data analysis and introduced a novel framework, PERForm, with innovative evaluation metrics. This framework was demonstrated on benchmark datasets such as Tox21, DILI, and MAQC.
2. Established a high-quality natural language processing (NLP) benchmark for scientific literature screening and developed specialized NLP models for research in chlorine and neurotoxicity. The NLP benchmark has facilitated future applications and enhanced the assessment of AI models' explainability and trustworthiness.

FDALabel

- FDALabel was updated to v2.9 as a collaborative effort between NCTR's Office of Scientific Coordination (OSC) and Division of Bioinformatics and Biostatistics (DBB), and FDA's CDER.
- NCTR hosted the Annual FDALabel Training for 577 participants. This two-day, FDA-wide virtual training event provided an overview, demonstrations, and real-world applications of FDALabel.

Read more about AI research at NCTR here.

Biomarkers

NCTR has representatives in the FDA Biomarker Working Group (WG) and inter-agency FDA-NIH Biomarker WG.

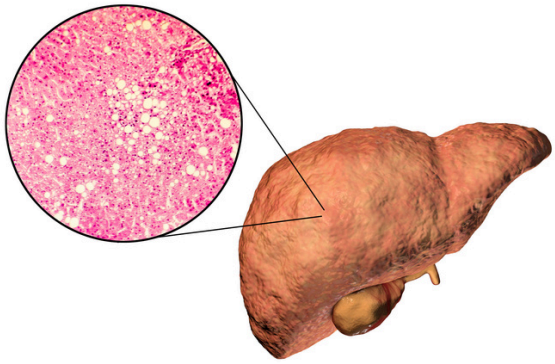
Clinical/Translational Omics Biomarkers

NCTR's Division of Systems Biology (DSB) OMICs branch conducts proteomic, metabolomic, lipidomic, and miRNA-omics studies to identify and validate biomarkers of toxicity and disease. In 2024, DSB scientists were involved in several clinical or translational omics biomarker projects:

- Leading a multi-center clinical study Informed Prediction of Anthracycline-induced Cardiotoxicity (IMPACT) to qualify candidate biomarkers of doxorubicin-induced cardiotoxicity.
- Developing a protocol identification of proteomic biomarkers of acetaminophen-induced hepatoxicity using stable isotope labeling (*Proteomics for Drug Discovery*).
- Patent submission (April 2024): "Baseline Proteomic Biomarkers and a Predictive Model for Identifying Breast Cancer Patients at High Risk for Chemotherapy-induced Cardiotoxicity." An associated manuscript is in revision.

NAFLD Biomarkers

NCTR scientists have been developing biomarkers associated with a susceptibility to Non-Alcoholic Fatty Liver Disease (NAFLD) and NAFLD-related liver carcinogenesis. Papers were published in *J Environ Sci Health C Toxicol Carcinog* and *Toxicol Appl Pharmacol*, and work related to this platform was presented at the 2024 Society of Toxicology (SOT) annual meeting.



Computer illustration of fatty liver disease

2024 RESEARCH THEMES

Cannabis-Derived Products

- NCTR researchers continued investigating potential toxicities associated with exposures to the cannabis plant component cannabidiol (CBD) and its two main metabolites, 7-hydroxy-CBD and 7-carboxy-CBD. Findings were published in multiple journals. Findings on human and mouse testicular Leydig cells and human hepatic cells, as well as a review of the metabolism and liver toxicity of cannabidiol, were published in 2024. In addition, the findings of an analysis of impurities in cannabis following vaporization was published.
- Another NCTR study investigated the impact of CBD use during pregnancy in a rodent model. Analyses of both behavioral and neurochemical tests did not reveal dose-dependent effects of perinatal CBD on offspring neurodevelopment. Data from this study was presented at the 2024 Developmental Neurotoxicity Society (DNTS) meeting.

Drug Compounding

NCTR supported CDER's Office of Compounding Quality and Compliance (OCQC) in drug compounding research, resulting in the following:

- enhanced reproducibility and improved methods for identification of compounds in complex mixtures of pharmaceutical ingredients (spectra) and accurate chemical analysis.
- efforts to standardize methods for sporicidal efficacy assessment and provide an accurate efficacy database for sporicidal products.

Data was presented at the ASM conference in June 2024.

Maternal & Perinatal Health

Perinatal Health Center of Excellence

With the support of collaborating product centers, NCTR coordinates the activities of the Perinatal Health Center of Excellence (PHCE) to conduct studies that address important perinatal regulatory-science needs.

In FY 2024, three new PHCE projects were awarded funding. Topics for these new projects include:

- Development of a quantitative systems pharmacology model for fetal cardiac safety
- Thrombosis in pregnant patients with sickle cell disease and the role and regulation of Von Willebrand Factor
- Evaluating the effect of obesity on the pharmacokinetics and pharmacodynamics of monoclonal antibodies in pediatric patients

2024 PHCE Accomplishments

- 13 second-year projects concluded in FY24.
- 3 first-year projects funded in FY2024 and will continue into FY25.
- 10 first-year projects were funded for FY25.
- Principal Investigators represented CBER, CDER, and NCTR in FY2024 and CBER, CDER, CDRH, NCTR, and OC in FY25.
- 5 articles published in Calendar Year 2024
- Collaborated with CDER to conduct safety assessments of morphine, methadone, and buprenorphine as treatment for neonatal opioid withdrawal syndrome (NOWS). A model of NOWS was established and preliminary findings presented at the 2024 Society of Toxicology annual meeting and a PHCE seminar.

Read more about maternal and perinatal research at NCTR here.

2024 RESEARCH THEMES

Nanotechnology

NanoCore

The Nanotechnology Core Facility (NanoCore), housed within NCTR's Office of Scientific Coordination, is equipped with instrumentation and laboratories that support FDA in understanding the physico-chemical characteristics, toxicity, and biological impact of nanoscale materials.

Nanotechnology Research and Scientific Breakthroughs

- The NanoCore received funding through an Interagency Agreement (IAA) from the National Institute of Environmental Health Sciences (NIEHS), Division of Translational Toxicology (DTT), to develop consensus standards prioritized through domestic and international stakeholder engagement to benefit the research community, regulatory agencies, and industry. In 2024, the NanoCore completed data analysis from three Interlaboratory Studies (ILS). The ILS resulted in data from 67 laboratories from 13 countries, and drafted final reports on data consistency, repeatability, and reproducibility, to be included in the three published standards. These are highly successful ILS—demonstrating the utility of the standards with < 5% Relative Standard Deviation—and meet the acceptance criteria of FDA bioequivalence and ICH guidelines. These standards were submitted to CDER for their Standards Recognition Program.
  - **ILS 1840**: Lipid Quantitation in Liposomal Formulations Using UHPLC-MS (17 Laboratories)
  - **ILS 1844**: Lipid Quantitation in Liposomal Formulations Using High Performance Liquid Chromatography (HPLC) with an Evaporative Light-Scattering Detector (ELSD) (15 Laboratories)
  - **ILS 1845**: Lipid Quantitation in Liposomal Formulations Using High Performance Liquid Chromatography (HPLC) with a Charged Aerosol Detector (CAD) (35 Laboratories)

- NanoCore scientists completed a project to elucidate the biodistribution and toxic potential of silver nanoparticles when introduced through female rat reproductive tract and published a peer-reviewed paper. This research is funded by FDA's Office of Women's Health and investigated the exposure of various forms of silver and their impact on reproductive tissues upon intravaginal exposure, including on tampons. This short-term, acute exposure study found that there is limited persistence of silver upon intravaginal exposure, with no significant pathological findings, albeit long-term studies were lacking in this area.

Read about NCTR's participation in FDA's 2024 NanoDay.

2024 Nanotechnology Select Publications

- "A Flow Cytometric Assay to Detect Viability and Persistence of *Salmonella enterica* subsp. *enterica* Serotypes in Nuclease-Free Water at 4 and 25°C." In: *Frontiers in Microbiology.*
- "Biodistribution and Toxic Potential of Silver Nanoparticles in the Female Rat Reproductive Tract." In: *NanoImpact.*
- "Chicken Juice Enhances *C. jejuni* NCTC 11168 Biofilm Formation with Distinct Morphological Features and Altered Protein Expression." In: *Foods*.
- "Exposure to a Titanium Dioxide Product Alters DNA Methylation in Human Cells." In: *Nanomaterials*.
- "Investigation of Sex-Based Differences in the Immunotoxicity of Silver Nanoparticles." In: *Nanotoxicology*.

Electron microscope image of Salmonella by NanoCore staff

- Significant global increase in plastic pollution is resulting in the formation of smaller pieces of plastics—called microplastics and nanoplastics—through degradation in the environment. These particles are omnipresent and are potential contaminants in food, seafood, and animal food and feed. NanoCore scientists collaborated within NCTR and FDA and published a regulatory science perspective on microplastics and nanoplastics analysis. NanoCore is also collaborating with other federal agencies and global regulatory entities to monitor research publications, develop guidelines, and conduct research for standardized methods appropriate for regulatory use.

Read more about nanotechnology research at NCTR here.

Nanotechnology (Cont.)

FDA and NCTR Support

- NanoCore scientists conducted a regulatory research study to identify the presence of lead chromate contamination in cinnamon samples through Scanning Electron Microscopy/Energy Dispersive X-Ray Spectroscopy mapping to detect co-localization (HFP and OII support).
- The NanoCore Electron Microscopy (EM) Facility provided Transmission Electron Microscopy support to understand the mechanism of viral interaction and entry into cells (DM support).
- The NanoCore EM Facility utilized Transmission Electron Microscopy to investigate the fate of silver and titanium dioxide nanoparticles in vitro using Transmission Electron Microscopy (DBT support).

Continuing Nanotechnology Research

- Study: "The Effect of Size, Surface, and Structure of Metallic Nanoparticles on Radiation Enhancement and DNA Damage in Cancer Cells," (A. Patri, PI). Significant progress has been made in the synthesis, surface functionalization, characterization, and developing new assay through Quart Crystal Microbalance for targeted binding functionality assessment. In vitro experiments ongoing.
- New Approved Concept: "Microplastics and Nanoplastics: A Concerted Collaborative Effort for Methods Development and Characterization of Real-World Samples and Mixtures," (A. Patri, PI). Protocol in development – collaboration with other Centers, Agencies, NIEHS/DTT.
- New Approved Concept: "Rapid Detection, Identification and Quantification of Foodborne Pathogens using Quantum Dot-Based Nanotechnology Platform" (G. Palui, PI). Protocol in development.

Bacteria Detected in Commercial Tattoo and Permanent Makeup Inks

DM scientists collaborated with scientists from FDA's Office of Cosmetics and Colors (OCAC) on a study to investigate the presence of anaerobic and aerobic bacteria in commercial tattoo and permanent makeup (PMU) inks. The manuscript "Detection of anaerobic and aerobic bacteria from commercial tattoo and permanent makeup inks" was published in *Applied and Environmental Microbiology*, a journal of the American Society for Microbiology (ASM) in July. The findings demonstrated that nearly half of the PMU ink samples and close to one-quarter of the tattoo ink samples tested contained bacterial contamination, even if the products were labeled "sterile."

Impact

This research contributed to a guidance issued by FDA to help tattoo ink manufacturers and distributors recognize and prevent situations in which tattoo or permanent makeup (PMU) inks may become contaminated: Insanitary Conditions in the Preparation, Packing, and Holding of Tattoo Inks and the Risk of Microbial Contamination (published October 2024).

This work was highlighted in a feature story by the American Society for Microbiology (ASM).

The Altmetric Attention Score—which takes into account the number of news stories citing the work, blogs, social media shares, etc.—for the publication is 1491 as of December 2024, which is in the top 5% "of all research outputs ever tracked by Altmetric."

Read the Research Highlight.

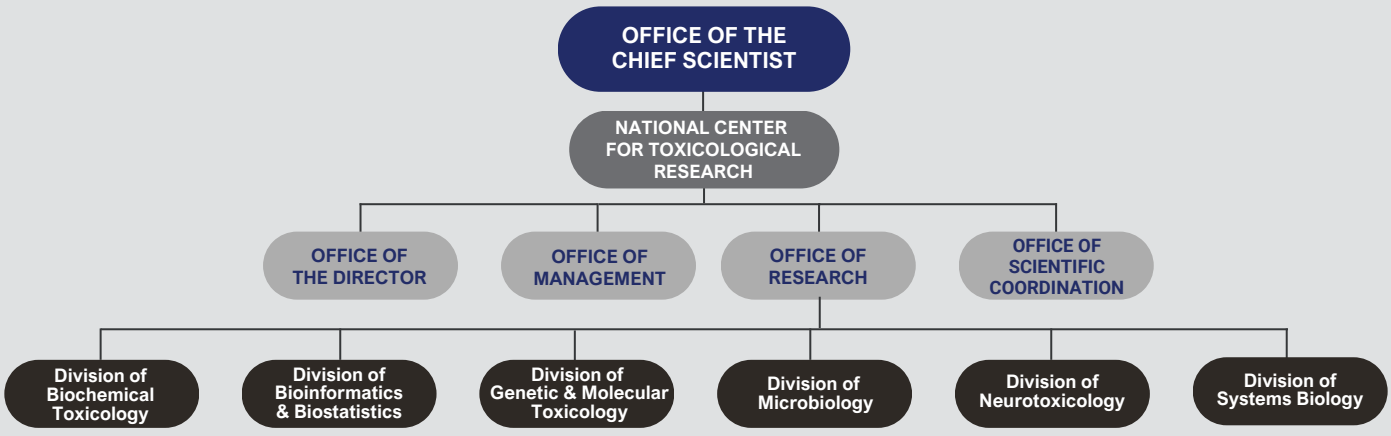
NCTR Organization

NCTR is organizationally located within FDA's Office of the Chief Scientist. NCTR is comprised of the following offices and divisions:

- Office of the Director
  - Regulatory Compliance and Risk Management
- Office of Management
- Office of Research
  - Division of Biochemical Toxicology
  - Division of Bioinformatics and Biostatistics
  - Division of Genetic and Molecular Toxicology
  - Division of Microbiology
  - Division of Neurotoxicology
  - Division of Systems Biology
- Office of Scientific Coordination

U.S. FOOD & DRUG ADMINISTRATION
National Center for Toxicological Research

FDA OFFICE OF THE CHIEF SCIENTIST ORGANIZATION CHART



OFFICE OF THE DIRECTOR

NCTR LEADERSHIP

NCTR Director — Tucker A. Patterson, Ph.D.
Senior Science Advisor — Gonçalo Gamboa da Costa, Ph.D.

NCTR's Office of the Director (OD) provides leadership and direction for all NCTR activities to ensure the Center's mission is accomplished. NCTR's mission is to address FDA's needs with high-quality research and serve as a global resource for collaboration, training, and innovative scientific solutions.

2024 OD Select Accomplishments

Research Highlights

Brominated vegetable oil (BVO) has been used as a food additive in citrus beverages to prevent citrus oils from floating to the top of the beverages. Previously conducted toxicological studies—in close collaboration with FDA's Human Foods Program under an Interagency Agreement with the National Institute of Environmental Health Sciences' Division of Translational Toxicology—to clarify specific outstanding questions on the toxicological profile of BVO resulted in multiple publications:

- 10.1016/j.foodchem.2016.06.110
- 10.1016/j.jchromb.2020.122415
- 10.1016/j.fct.2022.113137

The outcome of these studies contributed to FDA's conclusion that the intended use of BVO in food was no longer considered safe and prompted the agency to revoke the authorization to use BVO in food in July 2024. NCTR's work was referenced in the final rule.

2024 OD Select Publications

- "Advancing Alternative Methods to Reduce Animal Testing: Emerging Approaches Show Promise for Regulatory Use." In: *Our Science Magazine*
- *"*Potential Value of Animal Microphysiological Systems*."* In: *ALTEX – Alternatives to Animal Experimentation*
- "Protecting Human and Animal Health: The Road from Animal Models to New Approach Methods." In: *Pharmacological Reviews*
- *"*Trust Your Gut: Establishing Confidence in Gastrointestinal Models – An Overview of the State of the Science and Contexts of Use." In: *ALTEX – Alternative to Animal Experimentation*

Dr. Patterson

- Co-chaired, with FDA Acting Chief Scientist Dr. David Strauss, the first session of the Global Summit on Regulatory Science titled, "Global Landscape of Digital Technology in Regulatory Science."
- Facilitated a roundtable discussion on Artificial Intelligence with the FDA Principal Deputy Commissioner, Dr. Namandjé Bumpus, and NIEHS Director, Dr. Rick Woychik, at the Arkansas Bioinformatics Consortium (AR-BIC) annual meeting. Over 200 participants were in attendance.
- Presented a "State of the Science" talk on September 10 at the FDA Foods Program Regulatory Science Conference.
- Provided the opening keynote on October 23 at the European Food Safety Authority (EFSA) Symposium: Data Readiness for Artificial Intelligence in Parma, Italy. The symposium explored the transformative impact of AI technologies within the food safety ecosystem.
- Participated in a Careers in Toxicology Panel Discussion during the South Central Chapter of the Society of Toxicology Fall Meeting in December.

Dr. Gamboa

- Served as NCTR's representative for the International Liaison Group on Methods for Risk Assessment of Chemicals in Food and Feed (ILMERAC). ILMERAC is a network of more than 25 governmental and intergovernmental organizations with activities in the food and feed space, and the network aims to enable coordination and explore synergies and collaborative opportunities to foster the protection of public health.
- Represented FDA — along with Karen Hatwell from HFP — in preparation of the *Federal Sustainable Chemistry Strategic Plan* report to Congress. This report was prepared under coordination of the National Science and Technology Council Joint Subcommittee on Environment, Innovation, and Public Health in response to congressional language in the FY21 National Defense Authorization Act. The report outlines an interagency strategic plan that aims to implement the vision articulated in its previous report, Sustainable Chemistry Report – Framing the Federal Landscape, released in 2023.

Office of Research

NCTR's Office of Research (OR) organizes, plans, and directs NCTR research programs in accordance with NCTR-wide strategic direction.

The NCTR Research 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 on the market.

OR LEADERSHIP

Deputy Director — Dana van Bemmel, Ph.D., MPH

NCTR Research Divisions

- Division of Biochemical Toxicology
- Division of Bioinformatics and Biostatistics
- Division of Genetic and Molecular Toxicology
- Division of Microbiology
- Division of Neurotoxicology
- Division of Systems Biology

BIOCHEMICAL TOXICOLOGY

Office of Research

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

DBT LEADERSHIP

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

2024 DBT Select Accomplishments

Multiple DBT Study Programs Awarded

- Non-alcoholic fatty liver disease (NAFLD) is a progressive liver disease that, if left untreated, may progress to more advanced forms of the disease, including non-alcoholic steatohepatitis (NASH), liver cirrhosis, and fibrosis. NAFLD is estimated to affect 38% of adults globally. A research program led by Dr. Igor Pogribny is investigating models of the disease to interpret its molecular pathogenesis. Two peer-reviewed papers were published in 2024 on a preclinical model of severe NASH and a human hepatocellular in vitro model of NAFLD. The research group effort, developed in collaboration with scientists from FDA's CDER, National Cancer Institute, and Texas A&M University, was recognized with a **2024 FDA Group Recognition Award**.
- Dr. Jia-Long Fang led DBT scientists to complete a research program on the dermal carcinogenicity of the antimicrobial agent triclosan. These studies were conducted under the National Toxicology Program (NTP) umbrella. The findings of the two-year dermal carcinogenicity mouse bioassay were reported in *Archives of Toxicology* and in an NTP Technical Report (TR-604). The peer-reviewed manuscript was awarded an **NCTR Scientific Achievement Award/Director's Publication Award**.
- Silver nanoparticles are used in a variety of consumer, healthcare, and industrial products due mostly to their anti-microbial properties. Dr. Tariq Fahmi led a team of DBT researchers to study the immune response to silver nanoparticles of peripheral blood mononuclear cells and plasmas from healthy human donors to investigate whether sex-based differences exist. The study findings were published in *Nanotoxicology*. A previous publication by the same team was awarded the **2024 FDA's Chief Scientist Publication Award for Significant Outreach Activity.**
- DBT researchers collaborated with FDA's Human Foods Program (formerly CFSAN), Center for Drug Evaluation and Research (CDER), and Office of the Commissioner to study cannabidiol and its main metabolites. The lead scientist, Dr. Si Chen, received the **2024 FDA Scientific Achievement Award for Excellence in Laboratory** and Dr. Yuxi Li received the **2024 NCTR Scientific Achievement Award/Director's Publication Award for an Emerging Scientist**.
- DBT authors received **Best Poster Award in the SOT Medical Device and Combination Product Specialty Section** during the 63rd Annual Meeting of the Society of Toxicology in Salt Lake City, Utah, in March. The abstract titled, "Evaluation of the Ability of the In Vitro Reconstructed Human Epidermis (RhE) Irritation Assay to Predict the Irritation Potential of Medical Devices Compared with the In Vivo Intracutaneous Reactivity Assay per ISO 10993-23," was authored by DBT and CDRH scientists**.**
- Dr. Suresh Nagumalli received the **FDA/NCTR Challenge Coin** for outstanding dedication and commitment in support of ongoing crucial pharmacokinetic analysis.

Dr. Tariq Fahmi (center) received the Chief Scientist Publication Award for Significant Outreach Activity

BIOCHEMICAL TOXICOLOGY

Office of Research

DBT by the Numbers

37 — **Publications**
- 33 manuscripts
- 4 review articles

26 — **Professional Memberships/Working Groups**
- 5 internal-to-FDA WGs
- 5 NCTR/Jefferson Labs committees
- 16 external WGs, committees, and professional societies

10 — **Projects Closed**

Completed projects on triclosan toxicity, pharmacokinetic analysis of nicotine, aerosol inhalation exposure chamber dev.

45 — **Collaborations**
- 5 – internal to NCTR
- 40 – with FDA and/or external partners in academia, government, or industry

2024 DBT Select Outreach

Conferences and Workshops

- American Association for Aerosol Research Annual Conference (presentation)
- American Association for Cancer Research (AACR) Annual Meeting (2 presentations)
- AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved (session chair)
- American Chemical Society (ACS) Fall 2024 Meeting (presentation)
- American Society for Virology (ASV) Annual Meeting (presentation)
- Annual FDA-Wide Student Scientific Research Day (poster/lightning presentation and project presentation)
- Arkansas Bioinformatics Consortium (AR-BIC) 2024 (poster committee)
- Congress of the European Societies of Toxicology Meeting (presentation and invited speaker)
- Environmental Mutagenesis and Genomics Society (EMGS) Meeting (org. comm. member, PR/comms chair, poster presentation)
- FDA Foods Program Regulatory Science (FPRS) Conference (4 presentations)
- FDA NanoDay Symposium (poster/lightning presentation)
- GSRS24 (3 poster presentations)
- NCTR Summer Student Research Program (SSRP) (committee members, mentors, *Lunch and Learn Symposium Series* organizer)
- SOT 2024 Annual Meeting and ToxExpo (12 presentations)

Other Outreach

- AACR Women in Cancer Research (chair, invited interview)
- Blacks in Government (BIG) (chair, National Health and Wellness)
- "Fourth draft interim position statement on bisphenol A TOX/2024/08" committee discussion, UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment meeting (invited observer)
- National Institute of Standards and Technology (NIST)-led Standards for Wastewater Surveillance Working Group (member)
- Organization of Economic Co-operation and Development (OECD) Expert Group in Skin Absorption (member); Test Guidelines and Guidance Documents (NCTR contact)
- Society of Toxicology (SOT)-FDA Colloquium on Emerging Toxicological Science on the "Current State of the Science: Toxicology of Cannabidiol and Other Cannabinoids." (co-chair)
- South Central Chapter of SOT Fall Meeting — Careers in Toxicology Panel Discussion (panelist)
- Tox21 Federal Consortium (member, management team)
- UAMS Systems Pharmacology and Toxicology (SPaT) Workshop (hosted UAMS attendees for a DBT tour, 4 oral presentations, poster presentation)

Editorial Positions in Scientific Journals

- *Data in Brief* (Section Editor: "Pharmacology, Toxicology, Pharmaceutical Sciences")
- *Food and Chemical Toxicology* (Editorial Board Member)
- *Food Safety — The Official Journal of Food Safety Commission of Japan* (Editor)
- *Frontiers in Genetics* (Associate Editor: "Toxicogenomics" specialty section).
- *Journal of Environmental Science and Health, Part C: Toxicology and Carcinogenesis* (Editor-in-Chief and Associate Editor)

BIOINFORMATICS & BIOSTATISTICS

Office of Research

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

DBB LEADERSHIP

Division Director — Weida Tong, Ph.D.

Bioinformatics

Branch Chief — Huixiao Hong, Ph.D.

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

Biostatistics

Branch Chief — Dong Wang, Ph.D

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

Scientific Computing

Branch Chief — Edward Bearden

Provides IT support to all of NCTR

Review-to-Research and Return (R2R)

Branch Chief — Joshua Xu, Ph.D.

Translates division research for regulatory application

2024 DBB Select Accomplishments

NCTR Uncovers Drug Interaction with UGT Enzymes as an Indicator of Drug-Induced Liver Injury

DBB scientists conducted a study to explore how interactions between drugs and non-cytochrome P450 enzymes might lead to drug-induced liver injury. Their findings—that drug interactions with UGT enzymes are a strong predictor of DILI risk—were published in *Hepatology* in July and will be featured on the cover of the journal's May 2025 issue. *Read the Research Highlight.*

AskFDALabel

DBB researchers proposed a general framework for adopting large language models (LLMs) and demonstrated the framework through AskFDALabel, a system customized to assist with drug labeling review. The findings, shared in *Regulatory Toxicology and Pharmacology*, show how AskFDALabel provides a more efficient, accurate, and reliable solution for extracting relevant information from drug labeling documents. *Read the Research Highlight*.

Extension of Indel Ground Truth for Cancer Reference Samples

DBB researchers led an international team of scientists in a comprehensive review of indels—small insertions or deletions—in cancer reference samples. This review intended to enrich the "truth" set of indels for benchmarking mutation calling methods, ensuring the safety and efficacy of genomic technologies used in clinical settings. This "truth" set of indels was used in a PrecisionFDA challenge, "NCTR Indel Calling from Oncopanel Sequencing Data Challenge." Several key factors impacting the performance of indel calling methods and pipelines were identified from the challenge results (*Scientific Reports* March, April).

Impact: The extended indel ground truth set (published in 2024) and the positive and negative truth sets (published in 2021) together established benchmarks that inform regulatory decisions regarding genomic technologies, ensuring the accuracy of genomic analyses and bolstering the FDA's commitment to quality control in clinical genomic technologies.

LabelComp

An efficient and accurate tool for drug labeling comparison is urgently needed for post-market surveillance, enabling the identification of added adverse events to product labeling after approval and facilitating the tracking of these additions over time. As part of the BERTox initiative, DBB scientists have successfully built a labeling comparison tool by integrating an AI-based adverse events recognition model. The team trained the custom language model on human prescription drug-labeling documents and fine-tuned it for the specific task of adverse-event identification. The model's tailored design enhances its capacity to navigate the specific context and structure of labeling documents, resulting in improved accuracy and efficiency. CDER reviewers have extensively tested and validated this LabelComp tool. A manuscript summarizing the validation results was published in *Drug Safety*. The tool not only ensures highly accurate and efficient tracking of adverse-event changes in drug labeling, but also plays an important role in maintaining drug safety.

BIOINFORMATICS & BIOSTATISTICS

Office of Research

DBB by the Numbers

48 Publications
- 36 manuscripts
- 9 review articles
- 1 book chapter
- 1 conference paper
- 1 letter to the editor

30 Conferences and Seminars
SOT Annual Meeting, GSRS24, AR-BIC, MCBIOS, Workshop on Cheminformatics Resources of US Government Organizations, Joint Statistics Meetings, FDA Scientific Computing Day, FDA Omics Day, and more.

116 Collaborations
- 67 – internal to NCTR
- 40 – internal to FDA
- 9 – external (academia, industry)

104 Poster and Oral Presentations
- 62 poster presentations
- 42 platform presentations (SOT, MCBIOS, ICNA, etc.)

7 Projects Closed
Completed projects on AI methods for food safety, xAI, data-mining strategies, database development, R2R support.

5 FDA and NCTR Honor Awards
- 2 FDA Group Awards – 2023 FDA Statistical Association Board, FDA IT Strategy Team
- 2 NCTR Awards: Group Recognition – SARITA Team; NCTR Director's Award – Crowdstrike JL Response
- 1 Overall Impact Award at AI for Regulatory Science seminar – BERTox team

2024 DBB Select Outreach

Conferences and Workshops
- 2024 Workshop on Cheminformatics Resources of US Government Organizations (co-organizer, section co-chair)
- AR-BIC 2024 (program organizing comm., section chair, editor for conference proceedings, presenters)
- FDA Omics Day 2024 (program organizing comm.)
- FDA Scientific Computing Day 2024 (presentation)
- GSRS24 (presentation, program organizing comm., collabathon organizers)
- International Conference on Neuroprotective Agents (ICNA) 2024 (oral presentation)
- Joint Statistics Meetings
- MCBIOS (co-organizer, editor for conference proceedings, section co-chair, oral presentation)
- SOT 2024 Annual Meeting and ToxExpo (11 posters, 1 oral presentation)

Editorial Positions in Scientific Journals
- *Experimental Biology and Medicine* (Assoc. Editor, Editorial Board)
- *Frontiers in Artificial Intelligence* (Assoc. Editor)
- *Frontiers in Big Data* (Assoc. Editor)
- *Frontiers in Bioinformatics* (Assoc. Editor)
- *Frontiers in Drug Safety and Regulation* (Special Iss. Guest Editor)

Notable Collaborations
- With **CBER research group** on developing a bioinformatics pipeline to analyze NGS data from Zika and Dengue virus-infected samples.
- With the **CDER Science and Research Investments Tracking Archive (SARITA) team** to retrieve the publications conducted by CDER authors, manage and analyze CDER reports and projects.
- With **CDER's Office of Surveillance and Epidemiology (OSE)**:
  - FDA Adverse Event Reporting System (FAERS) database report deduplication analysis
  - Drug-event pair causality assessment
  - AI4PharmacoVigi project to establish an AI-based literature screening and reviewing platform (also with **FDA's Office of the Commissioner/Office of Digital Transformation).**
- With **NCTR Division of Systems Biology** on cardiotoxicity for cancer drugs (*Tox Sci*).

GENETIC & MOLECULAR TOXICOLOGY

Office of Research

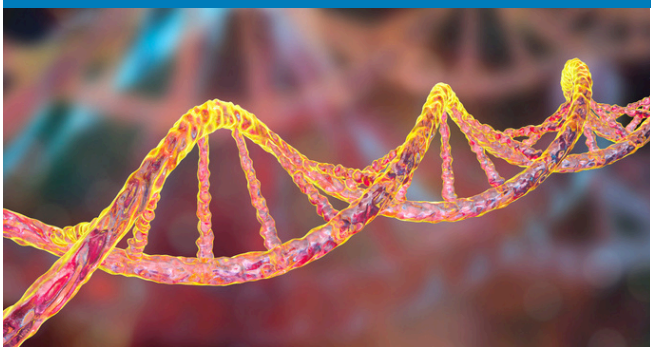
NCTR's Division of Genetic and Molecular Toxicology (DGMT) aims to improve public health by providing FDA with the expertise, tools, and approaches necessary for the comprehensive assessment of genetic risk.

The division goals include:

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

DGMT LEADERSHIP

Division Director — Robert Heflich, Ph.D.
Deputy Director — Mugimane Manjanatha, Ph.D.



2024 DGMT Select Accomplishments

Application of Error-Corrected Next Generation Sequencing Method for Quantification of Genomic Damage in Rats

DGMT scientists used duplex sequencing (DS) as an error-corrected next-generation sequencing (ecNGS) method that can detect ultralow-frequency mutations in rats. Genomic DNA from livers of rats exposed to a known mutagenic carcinogen—aristolochic acid—and a known nongenotoxic carcinogen—methapyrilene—were evaluated using the DS method. The mutation frequency for the aristolochic acid-treated group was significantly increased over the vehicle control (44-fold), whereas no significant difference in the mutation frequency was observed between the methapyrilene-treated and the control groups. The primary type of mutation induced by aristolochic acid was A:T > T:A transversion, whereas the major type of mutation in the control and methapyrilene-treated groups was G:C > A:T transition. These findings were consistent with published data obtained with other in vivo mutation assays. These results suggest that the DS mutation assay is a promising technology for assessing mutagenicity of chemicals in vivo.

Induction of Somatic Mutations in Organotypic Airway Cultures for Evaluation of Cancer Driver Mutations

DGMT scientists established a human in vitro organotypic air-liquid-interface (ALI) airway tissue model that is structurally and functionally similar to the human large airway epithelium. Human epithelial tissue models were treated with a known mutagen—ethyl methanesulphonate (EMS)—for 28 days, followed by a 28-day recovery period. Mutagenesis was evaluated by DS, and clonal expansion of bronchial-cancer-specific cancer-driver mutations (CDMs) was investigated by CarcSeq, a method for evaluating the clonal expansion of CDMs as a biomarker of cancer induction. EMS exposure led to time-dependent increases in mutagenesis over the 28-day treatment period, without expansion of clones containing lung-cancer-specific CDMs. A publication describes their work in detail.

Notable Collaborations

- DGMT and DBT researchers collaborated with CDER scientists to extend the application of CarcSeq method to detect clonal expansion of *Pik3ca* H1047R mutants caused by the non-genotoxic carcinogen—lorcaserin—in rat mammary tissues. CarcSeq is an ecNGS technique developed at NCTR to quantify expansions of CDMs. Findings were published in *Toxicological Sciences*.
- DGMT scientists collaborated with FDA's Center for Veterinary Medicine (CVM) to evaluate the genotoxicity of hydroxychloroquine, an anti-malaria drug recently promoted for treating or preventing COVID-19. Tests were conducted on human TK6 cells engineered to express different cytochrome P450s. The study showed that, although hydroxychloroquine was a weak mutagen, the drug was a potential risk to human health.
- DGMT researchers and University of Arkansas for Medical Sciences (UAMS) clinicians successfully evaluated *PIG-A* mutant frequencies in blood from cancer patients who were treated with the antineoplastic drug, cisplatin. The study concluded that cisplatin chemotherapy induces moderate increases in *PIG-A* mutant frequency in blood from head and neck cancer patients and that the *PIG-A* mutagenicity measured in the blood may serve as a tool for predicting adverse outcomes of genotoxic antineoplastic therapy.

GENETIC & MOLECULAR TOXICOLOGY

Office of Research

DGMT by the Numbers

16 — **Scientific Reports**
- 16 scientific reports published
- 4 manuscripts in press

16 — **FDA and NCTR Honor Awards**
- 2 FDA group awards
- 1 Commissioner's Special Recognition award
- 7 NCTR awards (including the NCTR Director's Award)
- 6 DGMT staff received special act/service awards

14 — **Internal Collaborations**
14 projects collaborated with other FDA Product Centers/Offices

45 — **Internal and External Working Groups**
- 13 FDA working groups, committees, and subcommittees
- 32 external working groups including the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

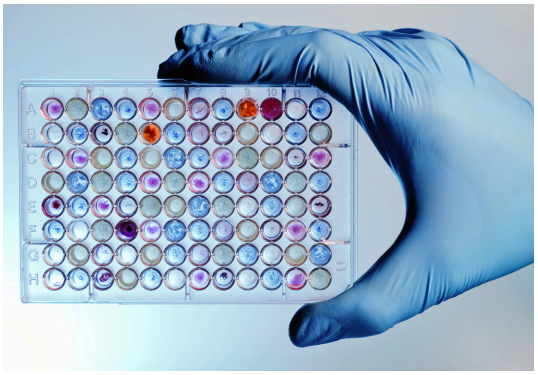
6 — **Intramural Funding Awards**
6 competitive intramural funding awards (CDER OND, CDER OPQ, CTP, NTP, PHCE [Co-PI])

27 — **Poster and Oral Presentations**
- 18 poster and 6 oral presentations at the annual Environmental Mutagenesis and Genomics Society and Society of Toxicology conferences
- 3 presentations at the UAMS Systems Pharmacology and Toxicology Workshop

DGMT Select Outreach

In 2024, DGMT scientists were invited to participate in different working groups and task forces:

- **Organization of Economic Co-operation and Development (OECD) Expert Group on Genetic Toxicology** and **Health and Environmental Sciences Institute/Genetic Toxicology Technical Committee (HESI/GTTC)** on advancement of genetic toxicology — submitted a proposal to the OECD to revise existing OECD genetic toxicology Test Guidelines.
- **International Agency for Research on Cancer (IARC)** — served as a panel member for a monograph review on the carcinogenicity of hydrochlorothiazide, voriconazole, and tacrolimus. The Working Group, comprising 22 scientists from 14 countries, began its review in March 2024. The evaluation process concluded in November 2024, culminating in the publication of their findings on the carcinogenicity of these substances in *The Lancet Oncology*.
- **8th International Workshop on Genotoxicity Testing (IWGT)** — DGMT scientists joined with scientists from academia, industry, and other regulatory agencies to publish a report on the use of mutation as a toxicological endpoint for risk assessment. The report—published in *Environmental and Molecular Mutagenesis*— details the findings and consensus-building efforts to improve the science of genetic toxicology.



- **CDER Nitrosamine Drug Impurity Task Force** — collaborated to enhance the bacterial Ames assay for detecting the mutagenicity of *N*-nitrosamine drug impurities and develop follow-up in vitro mammalian cell assays as well as use transgenic rodent mutation assays for confirming Ames assay results. The findings from the project are discussed at monthly meetings with the CDER *N*-Nitrosamine Drug Impurity Task Force and have contributed to two guidance documents issued by FDA/CDER (updated in 2024) and other regulatory agencies on how best to evaluate the mutagenicity of *N*-nitrosamine drug impurities:
  - CDER Nitrosamine Impurity Acceptable Intake Limits
  - Control of Nitrosamine Impurities in Human Drugs

  In addition, DGMT staff collaborated with scientists from CDER and HESI/GTTC by testing several *N*-nitrosamines as part of a multi-lab project with other research organizations and industry stakeholders.

MICROBIOLOGY

Office of Research

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

2024 DM Select Accomplishments

Bacteria Detected in Commercial Tattoo and Permanent Makeup Inks

DM scientists collaborated with scientists from FDA's Office of Cosmetics and Colors (OCAC) on a study to investigate the presence of anaerobic and aerobic bacteria in commercial tattoo and permanent makeup (PMU) inks. The manuscript "Detection of anaerobic and aerobic bacteria from commercial tattoo and permanent makeup inks" was published in *Applied and Environmental Microbiology*, a journal of the American Society for Microbiology (ASM) in July. The findings demonstrated that nearly half of the PMU ink samples and close to one-quarter of the tattoo ink samples tested contained bacterial contamination, even if the products were labeled "sterile."

Impact

- This research contributed to a guidance issued by FDA to help tattoo ink manufacturers and distributors recognize and prevent situations in which tattoo or permanent makeup (PMU) inks may become contaminated: Insanitary Conditions in the Preparation, Packing, and Holding of Tattoo Inks and the Risk of Microbial Contamination (published October 2024).
- This work was highlighted in a feature story by the American Society for Microbiology (ASM).
- The Altmetric Attention Score—which takes into account the number of news stories citing the work, blogs, social media shares, etc.—for the publication is 1491 as of December 2024, which is in the top 5% "of all research outputs ever tracked by Altmetric."

Read the Research Highlight.

DM LEADERSHIP

Division Director — Steven Foley, Ph.D.

Plasmid Analyses Toolbox

DM scientists examined the genetics and function of plasmids—genetic features that can often transfer from one bacterium to another, potentially transmitting antimicrobial resistance and pathogenicity-associated factors. These pathogenicity or virulence factors can increase the likelihood that a pathogen simultaneously colonizes a host and avoids immune system clearance, becoming resistant to antimicrobial treatment. This project provided valuable information and genetic tools to help understand the potential for the spread of antimicrobial resistance, increased virulence, and colonization potential among bacteria. Because of their biological importance, understanding the function of plasmids and their encoded genes will facilitate the development of better methods to prevent the spread of enhanced pathogens through the human food supply. The study generated tools that provided methods to determine the function of poorly characterized genes on plasmids to help understand their functions to evaluate the potential to impact human health. Manuscripts describing the tools developed were published in *Microbiology Spectrum* (paper 1 and paper 2) and data analyses in *Scientific Reports* and *Frontiers in Artificial Intelligence*.

Read more in the Antimicrobial Resistance section in our report.

MICROBIOLOGY

Office of Research

DM by the Numbers

22 Publications
- 19 manuscripts
- 3 review articles

19 Conferences and Seminars
12th AAVM, ASM Microbe, American Society for Virology annual meeting, AR-BIC, FDA Foods Program Regulatory Science Conf., FDA NanoDay Symposium, FDA Omics Days, GSRS24, MCBIOS, MPS Summit, SOT Annual Meeting

36 Collaborations
- 10 – internal to NCTR
- 18 – internal to FDA
- 8 – external (academia, industry)

38 Poster and Oral Presentations
- 27 poster presentations
- 11 platform presentations (FDA Grand Rounds, MCBIOS, AAVM, KoSFoS, Joint Agency Microbiome Working Group, etc.)

6 Projects Closed
Completed projects on biofilm models, 3D tissue culture models, bacterial detection in tattoo inks, and antimicrobial-resistant *Salmonella enterica*

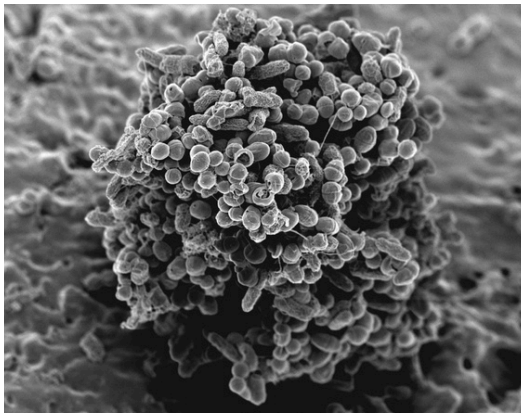
7 FDA and NCTR Honor Awards
- 2 FDA Group Awards
- 2 NCTR Scientific Achievement Awards: Director's Pub. Award for Translational/Applied Science; Outstanding Inter-center Scientific Collab.
- NCTR Director's Award
- NCTR Group Recognition Award
- ASM Peggy Cotter Award, ASM S. Central Branch

2024 DM Select Outreach

- 8th Microbiome Movement Drug Development Summit (presenter)
- 12th Intl. AAVM (platform and poster presenters)
- ACS (lecturer)
- AR-BIC 2024 (program organizing comm., presenter, poster contest winner)
- Arkansas Children's Hospital Research Institute Summer Science Program (presenter)
- Arkansas STRIVE Summer Program (mentors)
- ASM Future Leaders Mentoring Fellowship Program (mentors)
- ASM Microbe (9 posters)
- ASM Joint Branch Meeting/South Central and KY-TN Branches (poster)
- ASV Annual Meeting (3 posters)
- FDA FPRS Conference (5 posters)
- FDA Grand Rounds (presenter)
- FDA NanoDay Symposium 2024 (poster)
- FDA Omics Day 2024 (program organizing comm., presenter, 2 posters)
- Gastrointestinal Tract XXI: Life, Death, and Disease (poster)
- Intl. Assoc. for Food Protection Annual Meeting (IAFP) (2 posters)
- Intl. Conf. on Food Safety/39th Annual Meeting of the Korean Society of Food Hygiene of Safety (KoSFoS) (presenters)
- Joint Agency Microbiome (FDA, NIST, NIH and USDA) WG (presenter)
- Joint FAO/WHO Meeting on Pesticide Residues (expert)
- MCBIOS (session chair)
- Microphysiological Systems (MPS) World Summit (session chair, poster)
- SOT 2024 Annual Meeting and ToxExpo (poster)
- UAMS College of Pharmacy Seminar Series (presenter)

Notable Collaborations

- National Toxicology Program
- FDA Human Foods Program
- FDA Office of Cosmetics and Colors
- CDER Office of Compounding
- CVM Office of New Animal Drugs and Office of Applied Science
- CBER
- CDRH
- University of Arkansas-Little Rock



This SEM image illustrates the formation of a biofilm by rod-shaped Escherichia coli *and coccoid-shaped* Enterococcus faecalis *cells in synthetic human urine media.*

NEUROTOXICOLOGY

Office of Research

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

2024 DNT Select Accomplishments

Development of Novel In Vitro Approaches

FDA is committed to decreasing the number of animals used in regulatory science, while simultaneously ensuring its high standard for safety. This requires evaluating new technologies and understanding how they may complement or even replace existing methodologies. One such method is microelectrode array (MEA). MEA uses a series of tiny electrodes to measure the minute electrical signals given off by brain cells grown in a dish. This allows researchers to model functional groups of neurons outside of a living organism. Because this approach observes how neurons function, as opposed to if they are just alive or dead (the most common endpoint in neurotoxicity assessments), it allows researchers to model more subtle deficits than traditional in-vitro models. DNT staff are evaluating MEA's sensitivity to pharmacological manipulations known to impact synaptic activity in the absence of cell death. Initial validation using human-derived cortical cholinergic, glutamatergic, and GABAergic neurons have been completed.

DNT scientists have also been working with microphysiological systems or organ-on-chips and human stem cells. The organ-chip systems allow for closer modeling of human physiology and brain function. Division scientists use this technology to study the effects of chimeric antigen receptor (CAR) T-cell therapy. CAR T-cells are used to treat certain cancers, but can cause severe side effects. The use of a brain-chip can aid in the study of CAR T-cell-induced neurotoxicity, as it could model human responses to these treatments which would be missed in rodents. Both the organ-on-chip and MEA projects are in line with the FDA's Predictive Toxicology Roadmap.

DNT LEADERSHIP

Division Director — John Talpos, Ph.D.

Neurodegenerative Disease

Due to improved longevity, the population of Americans with neurodegenerative disorders like Alzheimer's and Parkinson's disease continues to increase. Division scientists recently published findings in *Current Alzheimer Research*, showing how a modified K114 staining procedure can detect amyloid plaques and tangles in both rat and human brains. This modified approach is quicker than standard methods and will allow for much quicker detection and analysis of Alzheimer's disease (AD) pathology in a laboratory setting. Additionally, this method is compatible with other immunofluorescent labeling, allowing the detection of AD-related pathology and other changes in the brain (e.g., cell death, neuroinflammation, vasculature changes) simultaneously.

Division scientists were awarded funding from the Office of Women's Health for a project entitled, "A sub-chronic and chronic geriatric female mouse model of Parkinson's disease: Evaluating the ITIS diet on reducing inflammation and improving L-DOPA drug metabolism and Parkinson's Disease outcomes by targeting the gut microbiome." This study will evaluate key interactions between inflammatory bowel disease and Parkinson's disease in post-menopausal women, and how inflammatory bowel disease impacts L-DOPA pharmacokinetics, the leading treatment for Parkinson's Disease. Work of this type is important to promote health equity.

NEUROTOXICOLOGY

Office of Research

DNT by the Numbers

5 — **Publications**
- 2 manuscripts
- 3 review articles

28 — **Poster and Oral Presentations**
- 18 poster presentations
- 10 platform presentations (ACT, DNTS, SEBM, SFN, SOT, SSC-SOT, ICNA,)

5 — **Projects Closed**
Completed projects on neurotoxicity biomarkers

35 — **Collaborations**
- 7 – internal to NCTR
- 28 – with FDA and/or external partners in academia, government, or industry

MRI T2 Relaxometry Biomarker Project

Measuring neurotoxicity in a living animal is difficult. Most methods to assess neurotoxicity require destruction of brain tissue. Part of DNT's mission is to develop noninvasive tools to assess neurotoxicity in life. For over a decade, DNT has been investigating if MRI T2 relaxometry can "predict" neurotoxicity in a living animal. A major milestone was achieved in 2024, when a letter of Intent (LOI) was submitted to CDER's Biomarker Qualification Program and formally accepted for biomarker qualification to use MRI T2 relaxometry as a guide for neuropathology in preclinical studies. This LOI represents a significant achievement not only for the division, but also for NCTR. Efforts continue to progress this package to full qualification.

2024 DNT Select Outreach

- American College of Toxicology (ACT)
- Developmental Neurotoxicology Society (DNTS)
- FDA's Alternative Methods Working Group
- ICNA
- Neurotrauma Diagnosis, Monitoring and Assessment State of Technology Meeting
- Society for Experimental Biology and Medicine (SEBM) annual meeting
- Society of Neuroscience (SFN)
- SOT Annual Meeting and ToxExpo
- South-Central Chapter of SOT

Noninvasive Assessments of Progressive Myeline Damage in a Model of Multiple Sclerosis

To advance the MRI T2 relaxometry project and investigate the utility of "fluidic" markers (those that can be found in blood, urine, saliva, etc.) of neurotoxicity, DNT scientists have been investigating the impact of cuprizone exposure on neurotoxicity. Cuprizone is known to negatively impact oligodendrocytes, an important type of cell that "insulates" brain cells. Division scientists were able to show that damage to these cells could be predicted by changes in blood levels of a protein called Neurofilament Light chain and by MRI T2 relaxometry. These data highlighted the potential of a fluidic and MRI-based biomarker approach while also developing a model of chemically induced multiple sclerosis. This work was done in collaboration with an international consortium of leading scientists that represent regulatory bodies such as CDER, CDC, EPA, and various industry and pharma partners. Additionally, this work was presented at this year's ICNA and ACT meetings.

DNT in the News

FDA cited an NCTR study of developmental toxicity and neurotoxicity of inorganic arsenic in a vertebrate alternative model using zebrafish under its predictive toxicology section (Closer to Zero: Reducing Childhood Exposure to Contaminants from Foods | FDA). Studies are ongoing on arsenic and cadmium mixtures in zebrafish to support this mission and FDA's initiative on NAMs. Based on the identified pathway (Sonic hedgehog signaling) of arsenic as a neurogenic agent in zebrafish, further interactive pathways were discussed relating to autism and arsenic in a review. Additionally, a publication on screening botanicals for safety assessment received national news coverage. This endeavor supports FDA's Botanical Safety Consortium, a collaboration established by the FDA, the National Institute of Environmental Health Sciences (NIEHS), and the Health and Environmental Sciences Institute (HESI).

Read the Research Highlight.

SYSTEMS BIOLOGY

Office of Research

NCTR's Division of Systems Biology (DSB) applies systems-biology approaches and innovative technologies to address regulatory research needs, knowledge gaps, and emerging health threats regarding:

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

DSB LEADERSHIP

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

2024 DSB Select Accomplishments

Therapeutic Safety & Product Center Support

DSB scientists continued to be integral contributors to the FDA Montelukast Working Group (MWG), founded in 2020 in collaboration with clinical and nonclinical staff from CDER/OND and led by Dr. Jessica Oliphant. Highlights from 2024 include the following:

- **Partnership** – The MWG served to facilitate cross-Center sharing of subject matter expertise in support of CDER/OND review work and NCTR/DSB research activities. The MWG continued studies applying multiple approaches to evaluate concerns of neuropsychiatric risks associated with montelukast (Singulair®).
- **Secondary pharmacology studies** were conducted that included two extensive off-target screening approaches and a battery of functional bioassays, which identified drug off-targets in the brain that are consistent with clinical reports of adverse neuropsychiatric events.
- **Presentations** — Dr. Oliphant shared the first public release of the results of the MWG studies as a Hot Topics presentation and poster during the 45th Annual Meeting of the American College of Toxicology.
- **Ongoing studies** to further assess the clinical translation of in vitro binding and functional data — Verification of biological activity in human brain cells downstream of off-targets, determination of drug and metabolite exposure levels in adult and juvenile rat brains, and evaluation of potential for drug accumulation in the brain.
- **External engagement** — The MWG collaborated with NCTR and OND communications staff to respond to numerous external requests from scientists, practitioners, media, lawmakers, and patient advocacy groups seeking information on the status of and results from DSB montelukast studies.

SpecID

SpecID is a mass spectrometry (MS)-based methodology developed by DSB scientists that entails a portable instrument capable of high-throughput, real-time, and direct analyses of a variety of sample types. In 2024, SpecID was used to:

- detect the presence of viral particles in saliva at very low levels (<500 virions/0.5 ml), classify coronaviruses, and distinguish SARS-CoV-2 variants (*PLOS One*).
- profile drug excipients present in Semaglutide drug products for CDER'S Office of Compounding Quality and Compliance (OCQC).

Oligonucleotide Drugs

DSB supported CDER's Office of Pharmaceutical Quality by conducting studies to address knowledge gaps regarding toxicological risks of impurities found in oligonucleotide drugs. Evaluation of hepatotoxicity of oligonucleotide impurities in human cells using NAMs revealed a greater degree of variability and potential risk for some impurities than previously expected in some donor cell lines. This work may help guide regulatory decisions regarding control of impurities for generic oligonucleotide products and was shared at an internal oligonucleotide subcommittee meeting.

Predictive Toxicology

- Due to concerns of potential human health risks associated with exposure to the environmental pollutant 6PPD-Quinone (6PPD-Q) through consumption of exposed fish, NCTR conducted liver toxicity studies in collaboration with HFP using a human cell-based in vitro approach. No significant hepatotoxicity was observed, suggesting that 6PPD-Q does not pose a human liver health risk at the anticipated exposure levels.

SYSTEMS BIOLOGY

Office of Research

DSB by the Numbers

Read more in the Biomarkers section of our report.

12 Publications
- 12 manuscripts published
- 4 manuscripts in press
- 6 internal study reports
- 3 internal consults (FDA Product Centers)

54 Internal and External Scientific WGs
- 29 FDA working groups (WG), committees, and subcommittees (SC)
- 20 external WGs
- 5 editorial boards for peer-reviewed scientific journals

22 Conferences/Symposia
- 7 international
- 4 national
- 3 public FDA
- 3 local public symposia
- 5 FDA SC & WG meetings

48 Posters and Oral Presentations
- 23 oral presentations (11 FDA-internal, 12 external)
- 25 posters (external conferences)
- 3 panelist and session chair/co-chair invitations

12 Intramural Funding Awards

8 competitive intramural awards (OWH, PHCE, OCS, MCMi) and 4 CDER funding awards

10 FDA and NCTR Honor Awards
- NCTR Director's Award
- FDA OC, CDER, and CVM Group Recognition Awards
- External Research Award
- 5 NCTR Special Act or Service Awards

Predictive Toxicology (Cont.)

- In collaboration with CDER, NCTR/DSB is in the process of assessing major commercial liver-on-a-chip platforms used to study of drug-induced liver injury. Cell sources and biomarker analysis protocols were identified as two critical factors affecting the reliability and reproducibility of findings based using on liver-on-a-chip technology. It was found that the sources of cells and the protocols for biomarker assays are two critical factors affecting the reliability and reproducibility of findings based on liver-on-a-chip technology. Using human iPSC-cardiomyocytes (hiPSC-CMs), donor-specific differences were found to be predictive of clinical inter-individual variability for doxorubicin-induced cardiotoxicity (DIC) and associated with a novel micro-RNA biomarker for DIC risk. Findings were published in *Toxicological Sciences*.

2024 DSB Collaborations

In 2024, DSB supported **66 research protocols** and **19 principal investigators**.

- 100% of the 66 active protocols had collaborators across NCTR, FDA, other government agencies, academic institutions or consortia, and industry.
- Most projects (80%) include subject matter expert collaborators at other FDA Centers or Offices.
- Nearly half (42%) include collaborations with other NCTR divisions or offices.
- Nearly 1/3 of DSB projects (29%) also include collaborators across 36 different external academic institutions or scientific consortia, 9% include collaborating experts at 8 other government agencies, both domestic and foreign, and another 9% have collaborators at 12 different industry groups.
- The 66 active research projects during 2024 included 248 individual collaborators.

Response to Health Threats/Emergencies

- Perinatal health studies were conducted using humanized mouse models of COVID-19, investigating the effects of SARS-CoV-2 and anti-viral therapy on fertility, pregnancy, and fetuses. Ongoing studies include evaluations in juveniles.
- Sex-based differences in susceptibility to variants of concern and coadministration of anti-viral and immunological therapies were also evaluated using in vivo COVID-19 mouse models.
- Metabolomics, lipidomics, miRNA-omics, and proteomics studies were conducted with COVID-19 patient plasma, which identified biomarkers and biological pathways associated with disease severity. Ongoing studies include immunoglobulin profiling associated with vaccine efficacy and breakthrough infections in patients.
- Proteomics analyses of bacterial strains causing gastrointestinal disease identified factors contributing to strain colonization potential (*Microbial Pathogenesis*).
- Identification of lipid biomarkers associated with latent *Leishmania* parasite infections contributed to an Employee Invention Report (May 2024): "A method to detect latent parasitic infections."

SCIENTIFIC COORDINATION

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

OSC LEADERSHIP

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

OSC Research and Support Services

Analytical Chemistry

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

Experimental Support

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

Microbiological Surveillance

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

Nanotechnology

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 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. *Read about more NCTR nanotechnology accomplishments*.

Statistics

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

Veterinary Services

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

SCIENTIFIC COORDINATION

OSC by the Numbers

22 Publications
- 9 manuscripts
- 1 review article
- 12 publications from other NCTR divisions with OSC support

12 Conferences and Seminars
2024 ASM Microbe Conf., ASTM Intl. E56 Nano Comm. (May and June mtgs), FDA NanoDay Symposium, GSRS24, Korea Research Institute of Standards and Science with Ministry of Food and Drug Safety Seminar, NanoKorea Conf., US-EU Communities of Research Mtg.

17 Memberships/WGs
- 3 – internal to FDA
- 14 – external

10 Poster and Oral Presentations
- 7 poster presentations
- 3 platform presentations (ASTM Mtg., EUROTOX 2024)

6 Projects Closed
Completed project on the Evaluation of the Migration and Toxic Potential of Silver Nanoparticles in Feminine Hygiene Products to Vaginal Tissue.

5 FDA and NCTR Honor Awards
- FDA Group Recognition – FDA Animal Care Programs
- NCTR Group Recognition Award – ORISE FDALabel Team
- CDER SBIA Group Award for leveraging and collaboration
- 2 OSC staff received special act/service awards

OSC Services (Cont.)

Onsite Support Contracts

NCTR maintains on-site contracts for animal care services, veterinary pathology services, and equipment maintenance services.

Animal Care Contract

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

Pathology Services Contract

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

Equipment Maintenance and Repair Contract

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

2024 Select OSC Accomplishments

Analytical Chemistry Unit
- Developed sensitive HPLC/MS/MS methods for the analysis of montelukast in rat plasma and brain samples (including the analysis of the concentrations in 9 separate brain tissue segments). (DSB support)
- Provided rapid turnaround for the investigation and testing of dose formulations for several cannabinoid test articles: cannabidiol (CBD), 7-OH-CBD, 7-COOH-CBD, and Tetrahydrocannabinol (THC); developed and applied sensitive HPLC/MS/MS methods for analysis in plasma (DSB support).
- Developed a quantitative method for the analysis of toxic metals (arsenic, cadmium, lead and mercury) using ICP tandem mass spectrometry to eliminate interferences from matrix effects.

Microbiological Surveillance Group — Developed an endotoxin assay that is now available to support research projects at NCTR.

Veterinary Services — Upgraded the Zebrafish facility with new racks and developed a breeding program to produce eggs available for studies in all NCTR research divisions.

FDA U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research

Contact

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