NCTR 2021 ANNUAL REPORT

NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH (NCTR)

1971 ~ The First 50 Years ~ 2021

To learn more about NCTR, visit

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TABLE OF CONTENTS

Message from the Center Director

The National Center for Toxicological Research (NCTR) is the U.S. Food and Drug Administration's (FDA) premier laboratory research center focused on all FDA-regulated products. NCTR's primary goal is to support FDA, a critical component of the Department of Health and Human Services (HHS), in its efforts to protect and promote the health of the American public.

NCTR holds a unique and foundational position at FDA because it is the only center that supports all FDA offices and product centers with the essential toxicological research and scientific data needed to conduct regulatory activities. NCTR's work has been critical to the development and evaluation of emerging toxicological methods and other new technologies that play such a large role in FDA's regulatory decision-making. Over the past year, NCTR staff have continued to generate and evaluate research data in the nation's fight against COVID-19. NCTR published 6 peer-reviewed COVID-19-related articles in 2021 and by the end of the year, NCTR had 14 active COVID-19-related projects with 13 additional projects in various phases of development. These projects have been developed to 1) describe rapid testing approaches for SARS-COV-2 and related viruses, 2) evaluate the developmental effects and ethnic disparities of viruses, 3) prioritize antiviral therapeutic repurposing, and 4) surveille wastewater for COVID-19 infections.

We invite you to learn how NCTR scientists are supporting the Agency in generating essential data and advancing the innovative tools and approaches that are vital to FDA's predictive capability and our ability to predict risk and efficacy.

After 44 years of working at the FDA's National Center for Toxicological Research and 16 years at the helm of NCTR, I will retire this year. Being director of NCTR has been the best job in the world because of the bright, inspiring, and dedicated researchers and staff I have had the privilege to work beside. So much has been accomplished and so much more is possible because of my fellow FDA employees. It has truly been a chance of a lifetime for over 40 years.

/s/

William Slikker, Jr., Ph.D.

Director, National Center for Toxicological Research

Click to listen as NCTR celebrates half a century of cutting-edge research.

NCTR Mission, Vision, and Research Goals

Mission

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

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.

Research Goals

1. Advance the scientific knowledge and research data required to support public health
2. Develop and evaluate the next generation of science and emerging technologies
3. Address emerging public health challenges, such as COVID-19
4. Collaborate with FDA product centers and offices to address issues of regulatory concern
5. Promote global outreach and collaborative research

Science Advisory Board to NCTR

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

The SAB to NCTR advises the Commissioner or designee in discharging responsibilities as they relate to helping to ensure safe and effective drugs for human use and, as required, any other product for which the FDA has regulatory responsibility.

2021 SAB Meeting

NCTR's 2021 SAB meeting was held virtually in May 2021 over two days.

Listen to the recording of SAB – Day 1

Listen to the recording of SAB – Day 2

More information on the 2021 SAB meeting can be found on the website.

NCTR at a Glance

Facilities

- 1 million square feet in 30 buildings
- More than 100 experimental laboratories
- Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)-accredited laboratories

NCTR Collaborations

- FDA Product Centers and Offices
- Academia and Medical Centers
- Government Agencies
- Industry

NCTR Expertise

- Analytical chemistry
- Antimicrobial resistance and pathogenicity
- Behavioral assessments
- Bioimaging
- Bioinformatics and biostatistics (datamining)
- Biomarker development
- Genetic toxicology assay development
- Neurochemistry
- PBPK modeling
- Reproductive and developmental toxicology

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

Most Impactful NCTR Accomplishments — First 50 Years

Take a look back with us as we reflect on some of NCTR's most impactful accomplishments in its first 50 years.

NCTR Leadership and Organizational Structure

William Slikker, Jr., Ph.D.
Center Director

Tucker Patterson, Ph.D.
Deputy Director for Research

Bradley Schnackenberg, Ph.D.
Associate Director, Office of Scientific Coordination

Gonçalo Gamboa da Costa
Senior Science Advisor, Office of the Director

Winona Cason (Retired October 2021)
Executive Officer, Office of Management

Rajesh Nayak, Ph.D.
Associate Director, Office of Regulatory Compliance and Risk Management

Donna Mendrick, Ph.D.
Associate Director Regulatory Activities

NCTR Division Directors

Frederick Beland, Ph.D.
Division Director, Biochemical Toxicology

Steven Foley, Ph.D.
Acting Division Director, Microbiology

Robert Heflich Ph.D.
Division Director, Genetic and Molecular Toxicology

William Mattes, Ph.D., DABT (Retired)
Division Director, Systems Biology

John Talpos, Ph.D.
Acting Division Director, Neurotoxicology

Weida Tong, Ph.D.
Division Director, Bioinformatics and Biostatistics

In memory of our friend and colleague, Dr. Carl Cerniglia, former Director of the Division of Microbiology

Outreach and Communications

NCTR: the First 50 Years, August 2021

NCTR celebrated its 50th anniversary with a hybrid virtual/in-person event. The celebration featured live and pre-recorded speakers that included Dr. Slikker, Jr., NCTR Center Director; Dr. Janet Woodcock, Acting FDA Commissioner; Asa Hutchinson, Arkansas Governor; RADM Denise Hinton, FDA Chief Scientist; Frank Yiannas, FDA Deputy Commissioner for Food Policy & Response; and U.S. Congressman Bruce Westerman. A new MOU between FDA and the State of Arkansas was signed at the conclusion of the ceremony. The event was held outdoors with a limited number of attendees on campus to adhere to COVID-19 guidelines. U.S. Representatives Westerman, Crawford, Hill, and Womack and U.S. Senators Boozman and Cotton introduced House (AR HR1047) and Senate resolutions recognizing the 50th anniversary milestone.

FDA Voices — FDA's National Center for Toxicological Research Celebrates Half a Century of Cutting-Edge Research, September 2021

An FDA Voices article was co-authored by NCTR Center Director, Dr. William Slikker, and FDA Chief Scientist, RADM Denise Hinton.

NCTR 360, Quarterly

The Communications Branch produced four new issues of the NCTR 360, an internal newsletter shared across FDA that covers a broad range of topics, such as individual successes, division accomplishments, informative articles, employee spotlights, hails and farewells, and upcoming events. The newsletter's high-quality content has increased two-fold since the inaugural issue in 2020.

Alliance for a Stronger FDA, October 2021

NCTR Center Director, Dr. William Slikker, delivered a virtual presentation to Alliance members, discussing NCTR's research priorities, accomplishments, and plans, and took questions from the Alliance members.

NCTR by the Numbers

One of the ways NCTR measures research performance is by tracking how much NCTR research is being published in reputable peer-reviewed scientific journals. Below are the publication numbers for 2019-2021.

Number of NCTR Publications (2019–2021)

2021 – 138

2020 – 132

2019 – 134

We also measure performance by tracking the number of subscribers who subscribe to the NCTR's public email lists:

FDALabel — periodic communications about updated versions and new features of the FDALabel application.

Global Summit on Regulatory Science (GSRS) — updates and announcements for the annual GSRS.

Jobs at NCTR — announcements of open positions at NCTR.

NCTR Bioinformatic Tools — updates on tools created at NCTR with the goal of developing methods for the analysis and integration of complex omics.

NCTR Research Highlights — brief summaries of NCTR research accomplishments and activities, research publications, and special events.

NCTR Science Insights — a newsletter sent periodically with a more comprehensive summary of NCTR research activities, accomplishments, collaborations, and special events.

2021 NCTR Email List Subscriptions: Number of Subscribers

Bioinformatic Tools – 38,835

FDALabel – 38,553

GSRS – 27,998

Jobs at NCTR – 25,827

Research Highlights – 48,549

Science Insights – 43,999

FDA-TRACK

FDA-TRACK is FDA's agency-wide performance management system that monitors FDA centers and offices through key performance measures and projects. NCTR has several key research projects and other related metrics that are tracked and published in FDA-TRACK. In 2021, the following projects were tracked:

I. Next Generation Sequencing (NGS) Project – Sequencing Quality Control Phase II (SEQC-II) ***(COMPLETED)***

II. Antimicrobial Resistance (AMR) Project – *Salmonella enterica* Virulence: Database and Analysis Tool Development and Validation Project ***(COMPLETED)***

III. Opioids and Other Ligands Project – Molecular Modeling of Opioids and Other Ligands Using a Three- Dimensional Multi-Target Approach Project ***(ON TRACK)***

Explore the progress NCTR is making towards its strategic priorities.

NCTR Research Collaborations

NCTR collaborative projects with FDA centers and other entities (academia, industry, other government organizations, etc.) in 2021.

NCTR Collaborative Projects – 2021 (as of 11/5/2021)

CBER – 7%

CDER – 36%

CDRH – 8%

CFSAN – 8%

CTP – 4%

CVM – 3%

Other (Academia, Industry, Other Government Organizations, etc.) – 34%

The coming pages will discuss a sampling of collaborative projects between NCTR and other centers or organizations. There are many acronyms and abbreviations, so we have provided a key below.

FDA Product Centers and Offices that Collaborate with NCTR

- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)
- Center for Drug Evaluation and Research (CDER)
- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Tobacco Products (CTP)
- Center for Veterinary Medicine (CVM)
- Office of the Commissioner (OC)
- Office of the Chief Scientist (OCS)
- Office of Regulatory Affairs

Examples of Organizations Outside of FDA that Collaborate with NCTR

- Organisation for Economic Co-operation and Development (OECD)
- National Institutes of Health (NIH)
  - National Center for Advancing Translational Sciences (NCATS)
  - National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/ NTP)
- National Institute for Occupational Safety and Health (NIOSH)
- University of Arkansas for Medical Sciences (UAMS)

Safety and Security at NCTR

Regulatory Compliance and Risk Management (RCRM) reports directly to the NCTR Director and is responsible for the overall safety and security of Jefferson Laboratories (JL) employees. The RCRM team also ensures that the research conducted at NCTR is compliant with all state and federal regulations and assists in the assurance of quality and integrity of the research data.

The RCRM compliance team is responsible for the following:

- Conducting comprehensive risk assessments of NCTR research protocols to ensure regulatory compliance in chemical, biological, radiological, and environmental safety.
- Maintaining inventories of hazardous chemicals and biological materials.
- Overseeing safety of employees under the medical and animal surveillance programs.
- Overseeing campus security (physical security, badging, fingerprinting, background clearances, etc.), records management, archiving, and quality assurance.
- Providing consistent, reliable, and excellent customer safety and security-related services to the JL campus and FDA.
- Providing safety updates through the JL Environmental, Safety and Health Committee meetings.
- Responding to emails, phone calls, and/or anonymous safety reporting.
- Providing necessary job-related safety training to employees and advising staff on personal protective equipment and safety programs such as hot work permits, confined space assessments, asbestos sampling, fire safety program, ReadyOp/FDA Alert system, fire/tornado drills, preconstruction building safety and security, Continuity of Operations (COOP), and occupant emergency plans.
- Supporting the FDA Office of Laboratory Safety (OLS) by assisting with and supporting their efforts to provide consistent and standardized guidelines, policies, procedures, and training across the Agency.
- Supporting the FDA Employee Safety and Occupational Health program organized under the Office of Facilities Engineering and Mission Support Services by providing occupational health and medical services to all government and contract employees, and research training program participants.
- Providing real-time data to OLS on lab safety inspections, safety training, employee occupational health and accident investigations/reports, environmental safety programs (e.g., chemical hygiene, hazardous waste management, chemical fume hoods and biosafety cabinets, and biosafety/bloodborne pathogen risk controls).

During the ongoing pandemic, RCRM's Occupational Health Unit nurses worked closely with the FDA Contact Tracing Team to assist staff and management on COVID- 19-related issues.

RCRM Agency Committee/Working Group Membership

- Environmental safety and health council
- Chemical safety
- Institutional biosafety council
- Biological safety and toxins safety
- Dual use of concern
- Radiological safety
- COVID-19 contact tracing program
- Institutional scientific collections
- Lab safety and security council and associated subcommittees
- Security operations and emergency management continuity of operations
- Good laboratory practices, quality resource and guidance, and human subject protection/ bioresearch monitoring
- Records liaison and reports clearances
- Jefferson Labs (JL) environmental safety and health, JL radiation safety, and JL animal welfare (IACUC, AAALAC, OLAW, etc.) committees

Contract Officers

RCRM team members serve as Contracting Officer Representatives for multiple contracts, including:

- Waste recycling
- Security
- NCTR-PBA Interagency Agreement (IAA)
- Medical laboratory services
- Physician services
- NCTR-ORA IAA
- Paper shredding
- Hazardous/medical waste disposal

Diversity, Equity, and Inclusion at NCTR

NCTR is committed to ensuring it continues to recruit, develop, and retain a diverse and inclusive workforce. In 2021, NCTR partnered with FDA's Scientific Staffing Team to bolster its recruitment efforts by partnering with colleges and universities, minority-focused professional organizations, veteran organizations, and STEM groups to attract more diverse talent.

NCTR continued to focus its employment and outreach efforts to increase applicant pools across underrepresented minority groups and advanced several initiatives designed to build a supportive, diverse, and inclusive workplace culture. These included such initiatives as:

- Leveraging "Schedule A" (a special appointing authority used to hire individuals with disabilities) to fill critical positions.
- Sharing the results of the Agency-wide Inclusion Survey with NCTR Senior Leadership and conducted briefings and information sessions with NCTR management to analyze the survey results and discuss strategies to increase employee perceptions of inclusion on campus.
- Participating in virtual job fairs at minority-serving institutions and the Little Rock Air Force Base.
- Highlighting diversity awareness with the "Faces of NCTR" campaign that shares employee profiles and hosts activities on campus corresponding with special-emphasis months, such as:
    - Hispanic Heritage
    - Black History
    - Asian and Pacific Islander
    - LGBTQ/Pride
    - Women's History
    - Veterans

On October 16, in celebration of Hispanic Heritage Month, a tamale lunch was served to employees on campus with Dr. Slikker providing opening remarks and Jefferson Labs employees enjoying approximately 450 tamales prepared for the event by one of NCTR's employees.

Facilities Improvement

The following updates to the Jefferson Labs campus at NCTR were started or completed in 2021.

Visitor's Housing and Conference Center (VHCC) Renovations

NCTR leadership collaborated with the local Office of Facilities Engineering & Mission Support Service (OFEMSS) team to plan a complete update of the interior of the dorms and conference center. The project plan included the services of an interior designer to ensure modern, innovative, and sustainable solutions. The newly-updated VHCC includes renovated kitchens and bathrooms, new flooring, and paint. The renovation work began late in 2020 and was completed in 2021. "We are excited about this upgrade and are appreciative of all the work our OFEMSS partners have done to ensure this is a first-rate facility," stated Winona Cason, Executive Officer.

Building 5 Renovation

Demolition in the interior of building 5D was completed and temporary partitions were built to allow access from building 5C to 5D's labs and mechanical rooms. The renovated 5D will eventually house Pathology Services, which is currently in the final design stages. The old roof was demolished and work on the new metal roof deck for building 5 began December 13, 2021.

Distributed Antenna System Update

Jefferson Labs campus implemented a Distributed Antenna System (DAS) to provide reliable cellular service throughout the Jefferson Labs campus buildings and centrally located outside areas. The following work was completed in 2021:

- A shelter installation by the drive-in gate.
- Running fiber from the shelter to the Center and between buildings.
- Installation of all antennas to support the

Select Awards in 2021

2021 ARA Fellow, Arkansas Research Alliance (ARA), April 2021
ARA Academy candidates represent a strategic value to advancing the research vision for their respective institutions. Each ARA Academy candidate is nominated by the director of their institution and after an external review, the ARA Board of Trustees approves each new ARA Academy member. *Laura K. Schnackenberg, Ph.D.*

SOCIETY OF TOXICOLOGY AWARDS

Toxicological Sciences Paper of the Year Award, March 2021
"Gene Expression and DNA Methylation Alterations in the Glycine N-Methyltransferase Gene in Diet-Induced Nonalcoholic Fatty Liver Disease–Associated Carcinogenesis"
Recipients: Barbara Borowa-Mazgaj • Aline de Conti • Volodymyr Tryndyak • Colleen R Steward • Leandro Jimenez • Frederick A Beland • Igor P Pogribny… and other co-authors.

Society of Toxicology Computational Toxicology Special Section (CTSS), March 2021

Postdoctoral Award
"Pregnancy PBPK Modeling of UGT Substrate Labetalol: An Application of Parameter Contribution Analysis to Guide Predictive Performance of Life-Stage Models"
Recipient: Kiara Fairman, Ph.D.

Best Abstract Award
Abstract Title: "Deep Learning-Powered Drug-Induced Liver Injury Prediction Using Model-Level Representation"
Recipient: Ting Li, Ph.D.

Abstract Title: "Elucidating Interactions between SARS-Co-V-2 Trimeric Spike Protein and ACE2 Using Homology Modeling and Molecular Dynamics Simulations"
Recipient: Suguna Dev Sakkiah, Ph.D.

Top 10 Abstract Awards
Recipients: Ting Li, Ph.D. • Suguna Dev Sakkiah, Ph.D. • Leihong Wu, Ph.D.

COMMISSIONER'S SPECIAL RECOGNITION AWARD

Office of Chief Scientist Training and Event Committee
Recipients: Donna Mendrick, Ph.D. ...and other FDA staff.

FDA GROUP RECOGNITION (CROSSCUTTING)

2020 FDA COVID-19 Contact Tracing Program Team
For exceptional performance and collaboration in developing and operationalizing a Contact Tracing Program to help prevent the spread of COVID-19 at all FDA facilities.
Recipients: Valerie E. Beck • Kimberly West ...and other FDA staff.

2020 FDA One Health, FDA
For exceptional performance and collaboration with stakeholders across disciplines to promote the health of humans, animals, and the environment using science, technology, and innovation.
Recipients: Tucker A. Patterson, Ph.D. ...and other FDA staff.

FDA Alternative Methods Working Group

For advancing science of alternative testing to develop more predictive methods that may also replace, reduce, or refine animal testing.
Recipients: William Mattes, Ph.D., D.A.B.T. • Donna Mendrick, Ph.D. ...and other FDA staff.

Focus Areas of Regulatory Science Committee

For working collaboratively to develop an evergreen, updated view of FDA's cross-cutting focus areas to advance regulatory science.
Recipients: William Mattes, Ph.D., D.A.B.T. • Donna Mendrick, Ph.D. ...and other FDA staff.

COVID-19 Testing for FDA Inspectional Activities Group

For outstanding performance in developing and operationalizing a first-ever COVID-19 testing program to ensure FDA's mission-critical inspectional activities during the COVID-19 pandemic.
Recipients: Valerie E. Beck • Kimberly West ...and other FDA staff.

Planning and Support Team for 2020 Scientific Computing Days

Recipients: Donna Mendrick, Ph.D. ...and other FDA staff.

EXCELLENCE IN LABORATORY SCIENCE, 2021 FDA SCIENTIFIC ACHIEVEMENT AWARDS

For a comprehensive body of research evaluating neurotoxic effects of general anesthetics on the developing central nervous system and the identification of predictive biomarkers.
Recipient: Fang Liu, Ph.D.

Human Hepatic Cell High-through-put Genotoxicity Assessment Group

For developing alternative human cell models for genotoxicity testing of FDA-regulated products.
Recipients: Matthew S. Bryant, Ph.D. • Xiaoqing Guo, Ph.D. • Mugimane G. Manjanatha, Ph.D. • Nan Mei, Ph.D. • Dayton M. Petibone, Ph.D. • Igor P. Pogribny, Ph.D. • Lijun Ren • Ji-Eun Seo, Ph.D.• Qiang Shi, Ph.D. • Volodymyr Tryndyak, Ph.D. • Qiangen Wu, Ph.D. ...and other FDA staff.

OUTSTANDING INTER-CENTER SCIENTIFIC COLLABORATION (GROUP)

FDA COVID-19 AI Drug Repurposing Team

For AI-powered drug repurposing for combating COVID-19.
Recipients: Xi Chen, Ph.D. • Zhichao Liu, Ph.D. • Weida Tong, Ph.D. • Dong Wang, Ph.D. ...and other FDA staff.

EXCELLENCE IN LABORATORY SCIENCE (GROUP)

Development of Human TK6-derived Cell Lines for Genotoxicity Testing For excellence of research to develop fourteen TK6-derived cell lines that stably expressing a single human cytochrome P450 for potential application in genotoxicity testing.
Recipients: Matthew S. Bryant, Ph.D. • Si Chen, Ph.D. • Lei Guo, Ph.D. • Xiaoqing Guo, Ph.D. • Xiaobo He, Ph.D. • Xilin Li, Ph.D. • Mugimane G. Manjanatha, Ph.D. • Nan Mei, Ph.D. • Qiangen Wu, Ph.D. ...and other FDA staff.

One Health Initiative

NCTR's One Health Initiative

One Health is a worldwide strategy to expand collaborations and communications around the connections shared between people, animals, plants, and environments. FDA collaborates with stakeholders across disciplines and sectors to promote the health of humans, animals, and the environment using science, technology, and innovation.

NCTR participated in the FDA One Health Symposium on April 13, 2021, and was represented by Dr. Steve Foley, Director of the Division of Microbiology. Learn more about FDA's One Health efforts and at 1:58 hear Dr. Foley discuss examples of NCTR's One Health-related research on antibiotic resistance.

Award: 2020 FDA One Health, FDA

For exceptional performance and collaboration with stakeholders across disciplines to promote the health of humans, animals, and the environment using science, technology, and innovation.

Recipients: *Tucker Patterson, Ph.D., and other FDA staff. (Awarded in 2021)*

2021 Global Summit on Regulatory Science (GSRS21)

The 2021 Global Summit on Regulatory Science was held virtually October 4-6, 2021, and was co-hosted by NCTR and the Global Coalition for Regulatory Science and Research. The theme for GSRS21 was "Regulatory Sciences for Food/Drug Safety with Real-World Data (RWD) and Artificial Intelligence (AI)." The conference hosted speakers from 10 countries and drew extensive participation (>800) from 46 countries during the three-day event, including Brazil, Canada, the European Union (EU), India, Italy, Japan, Switzerland, Singapore, and the United States. Discussions on the first day of the conference focused on digital health and safety, and discussion centered around AI and RWD for drug/food safety. On the second day, discussions focused on Artificial Intelligence and Machine Learning. By taking advantage of the virtual format, two new sessions were added to the GSRS program — the debate sessions and workshop.

- Opening remarks by Acting FDA Commissioner, Dr. Janet Woodcock.
- Keynote speaker presentation by Frank Yiannas, Deputy Commissioner for Food Policy and Response, FDA.
- Keynote speaker presentation by Stephen Quest, General Director at Joint Research Center, EU.
- Platform presentations from scientists across the globe.
- A live debate on the topic, "Is Regulatory Science Ready for AI?"
- A workshop showcasing data-science tools currently in regulatory use by FDA, the European Medicines Agency (EMA), and Swissmedic.

The annual GSRS is sponsored by the Global Coalition for Regulatory Science Research which is comprised of regulatory-science leaders from around the world. NCTR's Director has served as the co-chair of the Coalition's executive committee since its inception and has worked with the Coalition to promote global interaction.

Despite the worldwide challenges from the COVID-19 pandemic, the virtual GSRS21 was a success with in-depth scientific presentations on AI and RWD for regulatory application. Conference attendance jumped from approximately 200 attendees at the previous in-person meetings to more than 800 attendees. Recordings of each presentation as well as the Q & A session — where research presenters answered participants' questions in real-time via chat — are available for viewing.

Manuscript for GSRS20 Published

A manuscript titled "Emerging Technologies and Their Impact on Regulatory Science" that summarized last year's GSRS20 was published in *Experimental Biology and Medicine* in November 2021. The publication represents many of the presentations by scientists from NCTR and other research entities at the virtual GSRS20. There were 48 co-authors from 27 different research institutes representing 13 countries that contributed to the publication.

Read more about GSRS here: www.fda.gov/globalsummit.

Artificial Intelligence and Bioinformatics

Opioid-Related AI

NCTR, in collaboration with NCATS and CDER, created the Opioid Agonists/ Antagonists Knowledgebase (OAK) using computer-based methods. OAK will be used to assist in the review and development of alternative pain-management products. FDA's Public Health Assessment via Structural Evaluation methodology, combined with OAK, will help FDA improve evaluation of opioid drug products. *Journal of Chemical Information and Modeling*.

Using AI for Data Review

- NCTR scientists harnessed AI technology to mine FDA documents for relevant information to enhance regulatory operations and applications. A new bioinformatics project uses AI-based Natural Language Processing for FDA documents, specifically FDA-labeling documents. FDA has historically generated and continues to generate a variety of documents during the product-review process, leading to a large inventory of review documentation. Applying AI to the FDA documents allows the Agency to harness scientific opportunities, helping to:
    - Improve the Agency's operation.
    - Develop science-based regulation of products containing AI components.
    - Communicate with the public for improved transparency.
- In a related effort, AI technology was used to assess the safety profile (SafetAI Initiative) of potential drugs (in Investigational New Drug [IND] applications) which may also assist FDA reviewers. Given its implications and applications on regulatory sciences, explainable AI models are being developed to facilitate the Agency's adoption and application of AI technologies in evaluating and regulating AI-based medical products.

FDALabel — An FDA Drug Labeling Search Tool

The FDALabel database is a web-based application used to perform full-text and customizable searches of over 140,000 human prescription, biological, over-the-counter, and animal-drug labeling documents. FDA Label was updated to v2.6 in 2021 in a collaborative effort between FDA's Center for Drug Evaluation and Research (CDER) and NCTR's Office of Scientific Coordination and Division of Bioinformatics and Biostatistics. The new features in this updated version provide users the ability to:

1. Search for route(s) of administration.
2. View links to reference listed drug labeling.
3. Access reference list of established pharmacologic classes.

Drug-Induced Liver Injury

NCTR, in collaboration with CDER, benchmarked and compared various computational methods to predict DILI-related factors in drug products. The goal of this project was to develop more accurate and reliable predictive models for DILI to support regulatory decisions during the review process, specifically the IND phase. *Journal of Hepatology*, *Environmental Research and Public Health*, *Scientific Reports*, and *Archives of Toxicology*.

For more info on NCTR Bioinformatic Tools and AI, visit http://www.fda.gov/nctrbioinformatics.

COVID-19 Research and Response

COVID-19 Projects and Publications

NCTR has 14 active COVID-related projects with 13 more projects in development. Six peer-reviewed articles were published in 2021, providing data to help address the challenges associated with COVID-19.

- *Biochemical features and mutations of key proteins in SARS-CoV-2 and their impacts on RNA therapeutics*
- *Can SARS-CoV-2 infect the central nervous system via the olfactory bulb or the blood-brain barrier?*
- *Conformational Changes of the Receptor Binding Domain of SARS-CoV-2 Spike Protein and Prediction of a B-Cell Antigenic Epitope Using Structural Data*
- *Elucidating Interactions Between SARS-CoV-2 Trimeric Spike Protein and ACE2 Using Homology Modeling and Molecular Dynamics Simulations*
- *Identification of Epidemiological Traits by Analysis of SARS-CoV-2 Sequences*
- *Informing selection of drugs for COVID-19 treatment through adverse events analysis*

COVID-19 Wastewater Surveillance

NCTR developed a method to detect SARS-CoV-2 in wastewater, yielding important data to support the COVID-19 response. Wastewater surveillance warns of its increased circulation in a community, complementing individual testing to give a faster snapshot of viral spread in a population. In 2021, this research was presented at the Science Advisory Board, the FDA Scientific Forum, and the American Society for Virology's 40th Annual Meeting, and a manuscript was published in *Frontiers in Artificial Intelligence*.

COVID-Related AI

In 2021, NCTR started an AI project with the OCS Medical Countermeasures Initiative to support efforts to effectively treat COVID-19 patients. Using computational drug-repositioning principles, the project aims to systematically survey and prioritize approved or investigational drugs for their potential to treat COVID-19. In addition, NCTR will develop with CDER an AI-powered network pharmacology approach to explore the potential of existing drugs to treat COVID-19 using over 3 million data points.

NCTR researchers and other FDA staff held a webinar in August 2021, "AI Use for Drug Repositioning." This topic has been a large focus for COVID-19 therapeutics. *Drug Discovery Today*.

NCTR Presentation at 2021 FDA Grand Rounds

Studies of SARS-CoV-2 NSP1 and Envelope Protein presented by Dr. Marli Azevedo, NCTR Division of Microbiology, discussed the SARS-CoV-2 genome organization and its comparison with other human coronaviruses, gave a brief overview of SARS-CoV-2 replication cycle and SARS-CoV-2 non-structural proteins and their known functions, and provided an in-depth overview of NSP1 and envelope protein functions.

Dr. Marli Azevedo presented the "Studies of SARS-CoV-2 NSP1 and Envelope Protein" at the FDA Grand Rounds on March 11, 2021. Click for recorded presentation.

Maternal and Perinatal Health

The focus of NCTR's **Virtual Center of Excellence for Perinatal and Maternal Pharmacology and Toxicology** — also known as the FDA Perinatal Health Center of Excellence (PHCE) — is on the perinatal period (the period-of-time including pregnancy, childbirth, and infant/child development), which is a vastly understudied population. PHCE works to fill knowledge gaps about safety, efficacy, or potential toxicity that currently exist during the perinatal period, with the goal to strengthen the scientific basis of decision-making for FDA-regulated products used during pregnancy and in premature infants, newborns, and children.

A PHCE-related poster entitled: "Evaluation of maternal toxicity in CF-1 mice following gestational opioid exposure" was presented at the 2021 FDA Science Forum in May. The poster summarized work highlighted from a current PHCE-funded project. To examine if maternal toxicity may contribute, mice were exposed to opioids during pregnancy and assessed for hypoxia (low oxygen levels in bodily tissues). Physiological changes indicative of maternal hypoxia were observed, which may be useful supplemental data regarding opioid risks during pregnancy.

Many drugs and other medical products provided to pregnant women, neonates, and infants are used off-label. For this reason, NCTR research is designed to stimulate robust efforts to provide faster, less expensive, and more predictive approaches and models, thus, leading the way to improved safety and/or efficacy of FDA-regulated products in these susceptible populations. One PHCE study (p. 39) examined the long-term consequences of early-life exposure to anesthesia. While it is known that early-life exposure to anesthesia can cause neuronal degeneration, no study has directly explored the associated lack of oxygen and its role in the damage. This study will provide better-quality data for FDA to use in its regulatory mission and possibly expedite the development of safer anesthesia regimens for use in a clinical setting.

Perinatal Health Center of Excellence (PHCE) — 2021

The PHCE Leadership Council, led by NCTR, funded 10 new proposals in addition to the 17 projects that were previously funded or completed. Current PHCE projects include principal investigators from CBER, CDER, CFSAN, CVM, and NCTR.

Select PHCE research topics include:

- Neonatal immune responses to vaccines
- Computer-based pregnancy models
- COVID-19 effects on pregnancy, prenatal, and postnatal development
- Drug labeling associated with pregnancy

Read more information about the PHCE and its progress.

Nanotechnology

Select Accomplishments

- Nano Day Virtual Research Symposium was organized by the FDA Nanotechnology Task Force (NTF) and held on October 8, 2021. The theme focused on COVID-19 with presentations on vaccines and diagnostics, along with other research presentations. Approximately 200 attendees participated in the sessions.

- The NCTR Nanotechnology Core (NanoCore) **(p. 42)** — with support from the National Toxicology Program (NTP) and stakeholder involvement from government agencies, academia, and industry — developed documentary standards for nanomaterial characterization methods through the American Society for Testing and Materials (ASTM) E56 subcommittee on Nanotechnology and ISO Technical Committee 229. Three standards were finalized in 2021:
    - *Cholesterol and Lipid Quantitation in Liposomal Formulations using High Performance Liquid Chromatography Separation with Charged Aerosol Detector*
    - *Cholesterol and Lipid Quantitation in Liposomal Drug Products using High Performance Liquid Chromatography Separation Evaporative Light Scattering Detection (HPLC-ELSD)*
    - *Standard Guide for Visualization and Identification of Nanomaterials in Biological and Nonbiological Matrices Using Darkfield Microscopy/Hyperspectral Imaging (DFM/HSI) Analysis*

- In collaboration with CDER, the NanoCore studied generic drug products containing nanomaterials and their in vivo efficacy in tumor-bearing animal models. Three batches of liposomal drug products from three different vendors were characterized using various analytical techniques. Drug concentration and release of drugs in vitro were analyzed for all nine samples. Comprehensive animal studies were conducted on mouse models with xenograft tumors to test for efficacy of these products from different manufacturers. These studies were completed in early 2021 and manuscripts are being drafted.

- The NanoCore has multiple active research projects funded by internal grant support, including studies on immunotoxicity evaluation of nanomaterial generated from prosthetic implants after radiation exposure (funded by Collaborative Opportunities for Reseach Excellence in Science grants program) and sex differences in immunotoxicity of nanomaterials (funded by the Office of Women's Health).

Tobacco Products

The collaboration between the Center for Tobacco Products (CTP) and NCTR provides the research data and findings to inform FDA's regulatory authorities within the Family Smoking Prevention and Tobacco Control Act to protect public health. The tobacco regulatory science conducted at NCTR can be summarized in the following research areas.

Inhalation Toxicology

Inhalation toxicology studies are important to evaluate the dose-response toxicity of inhaled chemicals that are found in tobacco products or that form during the combustion process. The CTP/NCTR Inhalation Toxicology Core Facility (InhaleCore) provides the technical expertise to conduct these inhalation studies in compliance with international test guidelines (e.g., Organisation for Economic Co-operation and Development, OECD).

In collaboration with CTP, the InhaleCore researchers studied animal biological responses using various toxicological endpoints after they were exposed in a well-defined environment via nose-only inhalation. The research outcomes provided data to better understand and quantify the adverse health risks associated with humans using tobacco products, thereby supporting the FDA mission of regulating tobacco products.

- The InhaleCore completed a series of inhalation toxicology studies on 4-(methylnitrosamino)-1-(3-pyridyl)-1- butanone (NNK), a human lung carcinogen found in cigarette smoke, and published three manuscripts reporting the results:
    - *Toxicokinetic and Genotoxicity Study of NNK in Male Sprague Dawley Rats Following Nose-Only Inhalation Exposure, Intraperitoneal Injection, and Oral Gavage*
    - *14-Day Nose-Only Inhalation Toxicity and Haber's Rule Study of NNK in Sprague-Dawley Rats*
    - *90-day Nose-Only Inhalation Toxicity Study of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in Sprague-Dawley Rats*

- The InhaleCore also initiated a series of nicotine inhalation studies in Sprague-Dawley rats. The first of these studies, a pharmacokinetic (pK) study using three routes of exposure (inhalation, intravenous, and oral) is nearing completion. Using the pK results from this study and published models in the scientific literature, NCTR and CTP modeling groups are collaborating to develop a rat physiologically-based pharmacokinetic (PBPK) model for nicotine.

Alternative Models for Toxicological Assessment

- Scientists from NCTR, in collaboration with CTP, developed a human air-liquid interface (ALI) airway tissue model to assess the toxicological and inflammatory effects of whole tobacco smoke (or tobacco smoke constituents) in an in vitro system. Two manuscripts describing the development of treatment protocols and resulting abnormalities of cigarette exposures on the ALI tissue model, and the miRNAs associated with impaired mucociliary clearance caused by cigarette smoke in the ALI airway tissue model were published: *Organ Toxicity and Mechanisms* and *Archives of Toxicology*. Current work is focused on expanding this model for the evaluation of other tobacco product types, including electronic nicotine delivery systems.

- In collaboration with CTP, NCTR modeled the dosimetry and key adverse responses in normal human lung bronchial epithelial cells and human-lung cancer cells treated with the known tobacco toxicant, acrolein. The study suggested that the cell susceptibility to acrolein exposure is closely associated with acrolein uptake and formation of glutathione-acrolein adducts. Researchers concluded that dosimetry analysis might be useful for computational modeling and risk assessment of acrolein using different test systems. *Environmental Toxicology and Pharmacology*.

Bioinformatics/Artificial Intelligence

NCTR and CTP collaborated to develop a novel artificial intelligence (AI)-based tool to search tobacco product applications seeking marketing authorization. This tool will allow CTP reviewers to extract information from raw data in applications, thereby reducing the manual workload and increasing productivity.

Scientific Societies, Associations, and Organizations

NCTR's 120 Principal Investigators hold office in or are members of scientific organizations including (but not limited to):

African Organization for Research and Training in Cancer
American Association for the Advancement of Science
American Association for Cancer Research
American Association of Chinese in Toxicology
American Association of Pharmaceutical Scientists
American Board of Toxicology
American Chemical Society
American College of Clinical Pharmacology
American College of Toxicology
American Society for Cell Biology
American Society of Health-System Pharmacists
American Society for Mass Spectrometry
American Society for Microbiology
American Society for Nutrition
American Soc. for Pharmacology and Experimental Therapeutics
American Society for Testing and Materials
American Society for Virology
American Statistical Association
Arkansas Association for Food Protection
Arkansas Bioinformatics Consortium
Arkansas Biotechnology Association
Arkansas Neural Stem Cell Coalition
Arkansas Pharmacist Association
Association of Clinical Biochemistry of India
Association of Scientists of Indian Origin
Association for Women in Science
Behavioral Pharmacology Society
Brazilian Society for Virology
Chinese Association for Food Protection in North America
COnsortium of METabolomics Studies (COMETS)
Drug Information Association
Endocrine Society
Environmental Mutagen and Genomics Society
Escherichia coli Coalition Group
European Association for Cancer Research
European Environmental Mutagenesis and Genomics Society
European Federation of Biotechnology
FDA Alternative Model Working Group
FDA Artificial Intelligence Working Group
FDA Comm. on the Advancement of Clinical & Scientific Educ.
FDA Emerging Sciences Working Group
FDA Genetics and Genomics Group
FDA Institutional Review Board
FDA Institutional Scientific Collections
FDA Regulatory Policy Council
FDA Scientific Computing Board
FDA Sequencing Quality Control Group
FDA Senior Science Council
FDA Standards Committee
Food & Agri. Org. of the UN and the World Health Organization
Genetic Toxicology Association
Global Coalition for Regulatory Science Research
Health and Environmental Sciences Institute
Indian Immunological Society
Indo-US Science and Technology Forum

Institute For In Vitro Sciences Technical Working Group
Institute of Food Technologists
International Agency for Research on Cancer
International Association for Food Protection
International Cardioncology Society
International Congress on Nanobiomedicine
International Congress of Toxicology
International Drug Abuse Research Society
Intl. Life Sciences Institute/Health & Env. Sciences Inst. (HESI)
International Society for Behavioral Genetics
International Society for Computational Biology
International Society of Infectious Diseases
International Society for the Study of Xenobiotics
International Union of Crystallography
Interagency Coord. Committee on the Validation of Alt. Methods
Japanese Society of Toxicology
Massive Analysis and Quality Control Society
Metabolomics QA and QC Consortium
Metabolomics Society
MidSouth Computational Biology and Bioinformatics Society
Mucosal Immunology Society
Nanotechnology Task Force National Coordinating Entity for Sustainable Chemistry
National Institute for Occupational Health and Poison Control, Chinese Center for Disease Control and Prevention
National Inst. of Environmental Health Sciences P42 Superfund
National Nano Initiative/Nano Env & Health Implications
National Power To End Stroke, SNPhA National Science and Technology Council
National System of Researchers (Mexico)
Neurotoxicity Biomarker Working Group (HESI/FDA)
One Health at FDA
OpenTox
Organization for Economic Cooperation and Development (OECD)/Expert Working Group on the Pig-a Assay
OECD/Expert Working Group on Bacterial Gene Mutation Assays
Royal Statistical Society
Safety Pharmacology Society
Sequencing Quality Control Consortium
Sigma Xi
Society for Neuroscience
Society of Toxicology
Teratology Society
Tuberculosis Structural Genomic Consortium
US-EU Communities of Research for Nano

2021 NCTR Research Divisions and Important Accomplishments

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.

NCTR Research Divisions and Offices

Biochemical Toxicology — Frederick A. Beland, Ph.D., Division Director

Bioinformatics and Biostatistics — Weida Tong, Ph.D., Division Director

Genetic and Molecular Toxicology — Robert Heflich, Ph.D., Division Director

Microbiology — Steve Foley, Ph.D., Acting Division Director

Neurotoxicology — John Talpos, Ph.D., Acting Division Director

Systems Biology — William B. Mattes, Ph.D., DABT, Division Director (Retired)

Scientific Coordination — Bradley J. Schnackenberg, Ph.D., Associate Director

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

Division of Biochemical Toxicology

About the Division

NCTR's Division of Biochemical Toxicology (DBT) conducts fundamental and applied research specifically designed to define the biological mechanisms of action underlying the toxicity of products regulated by, or of interest to, the centers of the FDA. This research is focused on measuring the toxicities and cancer risk related to specific chemicals and introducing new techniques that enable regulatory agencies to better evaluate the risks associated with chemical exposure. The risk-characterization research is firmly rooted in mechanistic and exposure studies focused on the understanding of toxicological endpoints. This approach allows greater confidence in the subsequent risk assessments.

Select DBT Accomplishments in 2021

Investigating Male Reproductive Toxicities Induced by Cannabidiol and Its Main Metabolites

Researchers at NCTR, in collaboration with scientists from the Center for Food Safety and Applied Nutrition, investigated potential male reproductive toxicities and their underlying mechanisms induced by cannabidiol (CBD) and its main metabolites — 7-carboxy-CBD and 7-hydroxy- CBD — using immortalized mouse Sertoli cells and primary human Sertoli cells. Study results showed that CBD inhibited cellular proliferation, disrupted the cell cycle, and altered the cytoskeleton organization. 7-Carboxy-CBD and 7-hydroxy-CBD also inhibited cellular proliferation and decreased DNA synthesis during S-phase of the cell cycle. Read the publication for more information about this research and its findings which will help the FDA better define safety concerns regarding CBD. *Food and Chemical Toxicology*.

Characterizing Metabolically Competent HepG2 Cells for Assessing Drug-Induced Liver Toxicity

In a previous study, NCTR scientists developed a battery of HepG2-derived stable cell lines that individually express 14 cytochrome P450s (CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, and 3A7). This work has now been expanded to characterize each cell line for its CYP expression and enzyme activity by measuring messenger RNA and protein levels and metabolite formation. The NCTR investigators demonstrated the metabolic stability and response robustness of each of the CYP-overexpressing HepG2 cell lines. These cells can provide a practical in vitro approach for 1) screening drug and chemical metabolism, 2) metabolism-associated drug toxicity investigations, and 3) drug-drug interaction studies. *Journal of Environmental Science and Health. Part C, Toxicology and Carcinogesis*.

Ongoing Research Projects

- Evaluation of brominated vegetable oil in SD rats
- Effects of the fibrinolytic enzymes nattokinase and lumbrokinase alone or in combination with aspirin in blood parameters
- Toxicokinetic profile and toxicity of high-molecular-weight polyethylene glycols in Sprague Dawley rats
- Thermal inactivation of *Staphylococcal enterotoxins* in milk
- Pharmacokinetic analysis of nicotine in Sprague-Dawley Rats
- Assessing epigenetic effects of nanoparticles in human cells

- Relationship between liver epigenomic phenotype and susceptibility to nonalcoholic steatohepatitis
- Stimulate innovation in clinical evaluations and personalized medicine to improve patient outcomes with triple negative breast
- Percutaneous absorption of the sunscreen component avobenzone
- Development of a first-generation in-house FDA pregnancy PBPK model-based tool to enhance the safety and efficacy of therapeutic agents in the perinatal period
- Development of an artificially intelligent virtual pregnant woman modeling suite to support regulatory decisions
- Fetal and neonatal toxicokinetics of the C6- fluorotelomer alcohol
- High-throughput functional screens and mechanistic analysis of microRNAs that regulate chemotherapeutic resistance in ovarian cancer
- The biodistribution and placental transfer of tattoo pigments applied to the dorsal skin of pregnant female SKH-1 mice
- Identification of the structures and development of in silico models for predicting the levels of pyrrolizidine alkaloids-DNA adducts
- Construction and characterization of metabolically competent HepG2 cells for assessing drug-induced liver toxicity **(p. 28)**
- Surveillance of SARS-CoV-2 in wastewater as a complementary tool to estimate the viral spread in Arkansas **(p. 20)**
- In vitro evaluation of male reproductive toxicities induced by cannabidiol and its main metabolites **(p. 28)**
- Pharmacokinetics of cannabidiol upon dermal exposure in rats
- Pharmacokinetics of cannabidiol and its major metabolites in pregnant Sprague-Dawley rats and their pups exposed orally to cannabidiol
- Flow cytometry analysis of anti-SARS-CoV-2 antibodies in human plasma
- Performance of 3D-bioprinted human skin equivalents for in vitro dermal absorption testing of FDA-regulated drugs and cosmetic ingredients used for dermal and transdermal applications
- Percutaneous absorption of the cosmetic contaminant 1,4-dioxane
- Assessment of the developmental reproductive toxicity of metformin and glyburide
- 14-day pilot and dose-range finding nose-only inhalation toxicity study of nicotine in Sprague- Dawley rats **(p. 23)**
- Assessing epigenetic effects of the human food additive, food-grade titanium dioxide, in vitro
- Genomic and genetic determinants of the susceptibility to non-alcoholic fatty liver disease (NAFLD) and NAFLD-related liver cancer

Division of Bioinformatics and Biostatistics

About the Division

The mission of NCTR's Division of Bioinformatics and Biostatistics (DBB) is to ensure that its activities relate to FDA's review process, its work with product centers continues to be strengthened, and its capabilities evolve to meet the current and future needs of FDA. The Division applies various tools such as Artificial Intelligence (AI), Machine Learning (ML), molecular modeling, real world data analytics, and chemoinformatics to address FDA's diverse needs in the areas of drug safety, drug repositioning, biomarker development, precision medicine, genomics, rare diseases, endocrine disruptors, and risk assessment. Additionally, the Division provides support at NCTR relating to 1) IT infrastructure, 2) data analytics for research, 3) managing commercial and in-house software tools, and 4) conducting training sessions on bioinformatics tools.

Overview of DBB Research

The Division's research programs are designed and aligned with its mission. Division research can be collectively organized in the following five focus areas: **COVID-19** — repurposing existing drugs for potential therapeutic options with bioinformatics which is funded by the FDA Medical Counter Measure Initiatives (MCMi).

1. **Regulatory Applications and Support**
   DBB continued its collaboration with CDER to develop and support tools such as:

   - Data Analysis and Search Host (DASH)
   - Breakthrough Therapy Designation (BTD)
   - Safety Policy and Research Team (SPRT)
   - Smart Template System (STS)
   - FDA drug labeling documents (FDALabel).

   The Division also supported ORA by developing Automated Laboratory Information System (ALIS) — a customizable system that can be tailored to the specific needs across all the ORA laboratories — and CTP in creating ASSIST4Tobacco, which uses Natural Language Processing (NPL) for deeper searching capabilities on tobacco-based products.

2. **Alternative Methods and Knowledge Bases**
   Alternative methods like computational modeling help to predict the safety and efficacy of FDA-regulated products. Knowledge bases help build such predictive models by collecting a variety of experimental data and computational models. In this area, the Division worked tirelessly to develop advanced Drug-Induced Liver Injury (DILI) prediction models for FDA-regulated products like drugs (or potential drugs) and dietary supplements. In two separate efforts, Opioid Agonists/Antagonists Knowledgebase (OAK) (p. 19) was developed for better managing Opioid Use Disorder and an open access platform (Molecules with Androgenic Activity Resource) for assessing the safety profile for chemicals in various food, supplement, or cosmetic products that may affect the endocrine system and cause hormonal dysfunction.

3. **Precision Medicine and Therapeutics**
   DBB continued its long-standing involvement with the Sequencing Quality Control Phase 2 (SEQC2) Consortium to evaluate regulatory applications of next-generation sequencing (NGS) and to develop statistical tools for precision medicine. For the fifth consecutive year since its inception, the consortium drew over 300 participants from more than 150 international institutes and organizations. Research including drug repositioning for rare diseases and ways to combat present and future pandemics resulted in publications in numerous prestigious journals including *Nature Biotechnology* and *Genome Biology*.

4. **Artificial Intelligence and Machine Learning**
   The study of Machine Learning tools, including Artificial Intelligence, remained at the forefront of the Division's research focus due to growing technological advances in the medical and food industries (**p. 19**).

5. **Real-World Data (RWD) and Real-World Evidence (RWE)**
   This relatively new focus area for DBB is in line with FDA's recent commitment to increase the use of RWD/RWE to complement randomized clinical trials and to improve the efficiency and accuracy of the evaluation for product efficacy and safety. Division researchers focused on the following RWD/RWE topics:

   - Investigated racial disparities in patients with heart failure admitted to critical care and its subsequent impact on their health.
   - Analyzed the safety profiles of various prescription nonsteroidal anti-inflammatory drugs (NSAIDs) to understand the difference in patient sexes (male vs. female) across the US population.
   - Continued studies to compute Charlson Comorbidity Index (CCI) for the American Indian community that provided a practical tool of benefit for healthcare practitioners in this community.
   - Developed an integrative model for assessing **(****p. 19****)** DILI risks for various drugs and supplements.

DBB projects and related works in 2021 have resulted in 30 peer-reviewed research and review articles and one book chapter, many of which will be key milestones in better achieving both NCTR's and FDA's missions.

Select DBB Projects in 2021

The Division is comprised of three research branches and one support branch: Bioinformatics, Biostatistics, Research to Review (R2R), and Scientific Computing. In 2021, the Division focused on harnessing the benefits of big data and AI to support and advance regulatory science. Some of the important projects conducted this year included:

- Informed drug selection and combination of FDA-approved drugs for COVID-19 treatment using AI.
- Study of drug-induced liver injury (DILI) to support FDA review. **(****p. 19****)**
- Development of knowledge base for opioid crisis. **(****p. 19****)**

- Performance characterization of different NGS technologies for precision medicine.
- Clinical implication of NSAIDs using real world data and AI.
- Supporting regulatory application requested by other FDA centers (e.g., CDER, CTP, and ORA).
- Submitted several proposals to the FDA intramural grant solicitation (e.g., chief scientist challenge grant, OWH, etc.) with a broad range of topics such as racial disparities in critical care patients, DILI risk associated with herbal medicine and dietary supplements, and computation strategies and approaches to combat COVID-19.

Division of Genetic and Molecular Toxicology

About the Division

The Division of Genetic and Molecular Toxicology (DGMT) is internationally recognized for its expertise in developing and validating genetic toxicity assays and in interpreting genetic toxicity findings for regulatory decision-making.

Select DGMT Accomplishments in 2021

Genetic Toxicity Testing Using Human In Vitro Organotypic Airway Cultures

DGMT scientists collaborated with CDER scientists to develop methods for evaluating the genotoxicity of inhaled substances in an organotypic human air-liquid-interface (ALI) airway tissue model. Fully differentiated human ALI airway cultures were exposed to ethyl methanesulphonate for 28 days, the induced DNA damage was measured by a high-throughput CometChip assay, and mutagenesis was quantified using Duplex Sequencing, an error-corrected next-generation sequencing method. The results indicate that an integrated 28-day study can be used to measure several important safety endpoints such as DNA damage, mutagenicity, and tissue-specific general toxicity in physiologically relevant human in vitro ALI airway cultures. *Environmental and Molecular Mutagenesis*.

Genotoxicity Evaluation Using Primary Hepatocytes Isolated from Rhesus Macaque

DGMT researchers, with scientists from NCTR's Division of Biochemical Toxicology and Division of Neurotoxicology, collaborated to develop a whole liver perfusion method to extract primary hepatocytes from the livers of non-human primates. The isolated primary macaque hepatocytes (PMHs) were treated with various compounds known to have different pathways of genotoxicity/carcinogenicity and the resulting DNA damage was evaluated using the high-throughput CometChip assay. The comet data were quantified using benchmark dose (BMD) modeling and the BMD_{50} values were compared with those generated from primary human hepatocytes (PHHs) in a previous study. The results showed that despite varying CYP450 enzyme activities, PMHs had the same sensitivity and specificity as PHHs in detecting the genotoxicity of various test articles. These results support the use of PMHs as a reliable surrogate of PHHs for evaluating the human genotoxic hazards. *Toxicology*.

Mechanistic Evaluation of Black Cohosh Extract-Induced Genotoxicity in Human Cells

DGMT scientists in collaboration with scientists from NIEHS and NCTR's Division of Biochemical Toxicology tested black cohosh extract (BCE), which is marketed to women as an alternative to hormone replacement therapy, for genotoxicity in human cell lines using comet assays. The results showed that BCE induces acute DNA strand breaks which are quickly repaired in TK6 cells, whereas DNA damage seen at 4 and 24 h may reflect apoptosis. The present study supports the theory that micronucleus formation due to BCE exposure mainly occurs through an aneugenic mode of action. *Toxicological Sciences*.

PacBio Sequencing Detects Genome- Wide Ultra-Low-Frequency Substitution Mutations Resulting from Exposure to Chemical Mutagens

DGMT scientists used PacBio Single-Molecule, Real-Time (PB SMRT) sequencing to detect substitution mutations caused by chemical mutagens in *Escherichia coli* by generating nearly error-free consensus reads after repeatedly inspecting the DNA sequence in both strands of

circular DNA molecules. PB SMRT sequencing detected mutation frequencies and spectra comparable to those obtained by clone-sequencing from the same exposures and demonstrated a sensitivity of detecting 1×10^{-7} mutations in *E. coli*. *Environmental and Molecular Mutagenesis*.

CarcSeq Used to Detect Biomarkers for Lung Cancer

DGMT scientists developed an error-corrected next-generation sequencing method, CarcSeq, and a mouse CarcSeq panel (analogous to human and rat panels) to quantify variation in levels of spontaneously occurring cancer driver mutations (CDMs). CarcSeq measures clonal expansion of CDMs to predict the future risk of neoplasm development. The study demonstrated that the median absolute deviation (MAD) measured in normal human lung DNA samples showed a correlation of moderate strength and borderline significance with age (a cancer risk factor), as well as age-related cumulative lung cancer risk, suggesting these MAD may inform species extrapolation from mouse to humans. *Toxicological Sciences*.

Recommendations for Conducting the Rodent Erythrocyte Pig-a *Assay*

DGMT scientists worked with scientists from Organisation for Economic Co-operation and Development (OECD)-member countries to provide recommendations for conducting the rodent erythrocyte *Pig-a* assay to measure in vivo somatic cell mutation. Their recommendations on best practices for designing and conducting rodent *Pig-a* studies in support of evaluating test substance safety are described in a report from a Workgroup of the Health and Environmental Sciences Institute/Genetic Toxicology Technical Committee. *Environmental and Molecular Mutagenesis*.

DGMT scientists are frequently asked to consult in evaluating genetic toxicology data and have hands-on expertise in conducting common regulatory genetic toxicology assays (e.g., Ames, TGR, Comet and Pig-a).

Ongoing Research Projects

- Genetic Toxicology Evaluations in Support of FDA Centers for Evaluating Substances for their Genotoxic Potential (CDER)
- A Validation Study of Vitrocell Exposure Systems to Investigate the In Vitro Toxicity of Electronic Nicotine Delivery Systems at the Air-Liquid Interface (CTP)
- Application of Human In Vitro Airway Tissue Models for Coronavirus Antiviral Drug Screening and Drug Repositioning (CBER, CDER)
- Developing an In Vitro System to Evaluate the Disease-Related Toxic Effects of Inhaled Test Agents in Human Airway Tissue Models (NTP-funded, CDRH)
- Assessing *Bordetella pertussis* Adhesion in an In Vitro Human Airway Epithelial Tissue Model (CBER)
- Development of an In Vitro Co-Culture System to Test the Adverse Effects of Drugs and Their Metabolites on the Human Embryo-Fetal Development (PHCE-funded, CBER)
- Development of a Microphysiological System for Evaluating Zika Virus Sexual Transmission Using a Non- Human Primate Testicular Model (MCMi-funded, CBER)
- Development of a Microphysiological System for Evaluating Antibody Therapies Targeting Viral Infections During Pregnancy: a Zika Virus Case Study (MCMi-funded, CBER)

Division of Microbiology

About the Division

The mission of the Division of Microbiology (DM) is to serve a multipurpose function with specialized expertise to perform fundamental and applied research in microbiology in areas of FDA's responsibility in toxicology and regulatory science. To meet this mission, the Division's projects involve multidisciplinary research approaches that address a variety of FDA issues with special emphasis on:

1. Evaluating the impact of antimicrobial agents, food contaminants, food additives, nanomaterials, and FDA-regulated products on the microbiome.
2. Developing methods to detect and characterize microbial contaminants in FDA-regulated products.
3. Determining antimicrobial resistance and virulence mechanisms of foodborne and other pathogens.
4. Conducting research to aid FDA in the areas of women's health, tobacco products, and nanotechnology.
5. Improving risk assessments of FDA-regulated products, including integrating systems-biology approaches.

Select DM Accomplishments in 2021

Food Safety and Virology: Antimicrobial Resistance and Virulence

- Assessed the contributions of bacterial plasmids to increased virulence and antimicrobial resistance in bacterial pathogens and evaluated factors that lead to dissemination of plasmids between bacteria, which could lead to more difficult-to-treat infections. *Frontiers in Microbiology* and *Microbiology and Molecular Biology Review*.
- Produced recombinant Coronavirus spike proteins that are important resources for ongoing evaluation of viral-host cell interactions and used computational approaches to assess changes in the receptor binding domain of the spike protein and predicted antigenic epitopes based on structural data of the protein. *Frontiers in Artificial Intelligence*.
- Carried out studies in partnership with the University of Arkansas at Little Rock to assess the antimicrobial properties of nanostructured aluminum foil surfaces generated using a simple hot-water treatment approach. There are potential applications for nanostructured food-contact surfaces to minimize spoilage and the growth of foodborne pathogens. *Nanotechnology* and *MRS Advances*.

Microbiome and Biological Interactions

- Assessed the impact of the exposure of antimicrobial drug residues on the human gastrointestinal-tract microbiota composition and intestinal permeability. Higher exposures were found to lead to alterations of the microbiota and intestinal permeability. *Antibiotics*.
- Continued studies on the of exposure of xenobiotic compounds, including arsenic, bisphenol AF, and triclosan on the microbiome and host responses through National

Toxicological Program-funded efforts. These efforts are informing risk assessments of the test compounds. *Toxicological Sciences*.

- Evaluated the exposure to different nanomaterials on the gastrointestinal tract and the microbiome. Increased numbers of products contain nanoscale materials, yet there are limited numbers of studies available describing the potential impact on microbial dysbiosis, inflammatory responses, and epithelial cell permeability following exposure to these types of compounds. *NanoImpact*, *Research Square*, and *International Journal of Molecular Sciences*.

Microbial Contaminants Detection

- Developed and evaluated a simple gene-amplification method for the detection of *Burkholderia cepacia* complex (BCC) in non-sterile pharmaceutical products. Improved and widely accessible detection methods for BCC is important to limit patient exposure to a potential set of BCC pathogens that have been linked to multiple disease outbreaks. *Pathogens*.
- Assessed the impact of different storage conditions of fecal specimens and the corresponding ability to detect the important pathogen *Clostridioides difficile*, which is the cause of difficult-to-treat infections in many patients. The ability to make an accurate diagnosis is key to developing effective treatment strategies for the infections. *Pathogens*.
- Used sequencing methods to characterize potential bacterial pathogens for both veterinary and human patients. *Microbiology Resource Announcements* (October 2021 and November 2021) and *Canadian Journal of Microbiology*.

Ongoing Research Projects

- A Recombinant Coronavirus Spike Protein to Generate Reagents, Study Cell Interactions and Antibody-Dependent Enhancement
- Discovery of Intracellular and Extracellular Signaling Pathways and Mechanisms Contributing to Complement Activation and Coagulopathies Associated with Coronavirus Infections
- Assessment of the Role that the Microbiome May Play in the Toxicity of Xenobiotics
- Multi-Lab Validation of Isolation and Identification of Nontuberculous *Mycobacteria* Associated with Tattoo-Related Skin Infections
- Detection of Microbial Contaminants, Including Anaerobic Bacteria, in Tattoo Inks and Other Related Products
- Establishing Standardized Methods for Sporicidal Efficacy Assessment and Building Up an Efficacy Database of Sporicidal Products to Support FDA's Regulation on Drug Compounding
- Evaluation of Antimicrobial, Antibiofilm and Cytotoxicity Activity of Nanoparticles (Se, V) and Nanostructured Surfaces (Ti, Cu) and Transcriptomic and Proteomic Response of Multidrug Resistant Bacteria
- Evaluation of Tools to Efficiently Assess Antimicrobial Resistance and Pathogenicity-Related Functions of Plasmids in Bacterial Pathogens
- Evaluation of In Vitro Vaginal Tract Models to Assess the Biotherapeutic Potential of *Lactobacillus* Toward Toxic Shock Syndrome Toxin-1 Producing *Staphylococcus aureus*

- Metagenomic Analyses for the Detection of Microorganisms in Non-Sterile Pharmaceutical Products

Division of Neurotoxicology

About the Division

The Division of Neurotoxicology (DNT) focuses on increasing FDA's understanding of the processes associated with neurotoxic outcomes — harmful effects associated with the brain and nervous system. This increased understanding may provide opportunities for improved risk assessments and identification of new approaches to diagnosis. The Division's strategy has been to use a broad range of research approaches that capitalize on the expertise of personnel in diverse areas of neuroscience and other scientific disciplines.

Select DNT Accomplishments in 2021

Cannabidiol (CBD) Exposure and Its Effects

An emerging focus within FDA is developmental toxicity associated with cannabidiol. In collaboration with FDA's Office of the Chief Scientist, DNT researchers began a multiple-year assessment of the effects of CBD early in life on brain development and cognitive performance in the rat. Additionally, researcers studied the possibility of early-life exposure to CBD altering the immune response later in life. These studies are expected to determine if the brain's "defense mechanisms" against infection and injury change in response to these exposures. Work will continue into 2022 and will fill data gaps and guide future regulatory decisions.

Developmental Toxicity of Inorganic Arsenic Exposure

Arsenic occurs naturally in groundwater and can find its way into various foods including rice, a popular ingredient in baby foods. NCTR researchers collaborated with CFSAN to complete a comprehensive assessment of the neurotoxic potential of early-life exposure to arsenic. In these studies, rats were used to model the human response to arsenic exposure. The effects of arsenic on behavior and brain development were assessed and will soon be published. These data will help inform the Agency on acceptable levels of arsenic exposure from food in children.

Blood-Brain Barrier (BBB)-Related Neurotoxicity

The brain is a sensitive organ and exists in a micro-environment maintained by the blood-brain barrier. Failure of the BBB will compromise this micro-environment and can lead to brain damage. In collaboration with the Office of Women's Health and NCTR's NanoCore (p. 22), DNT scientists investigated sex-linked differences in inflammation change in the BBB's response to Alzheimer's disease. Specifically, the impact of sex on BBB function, disease progression, and cognitive function were assessed. To complement these animal studies, "brain-on-a-chip" technology was used to better understand the mechanisms behind BBB dysfunction. The Division also took delivery of a new inverted live-cell imaging confocal microscope to enable assessments of BBB function and other neurotoxicity endpoints.

Using Zebrafish Model to Explore Arsenic- Related Neurotoxicity

The rat is a powerful and predictive research model but is slow compared to alternative research models. In collaboration with the Perinatal Health Center of Excellence (PHCE), researchers in the Division used the zebrafish to explore how arsenic causes neurotoxicity. This work will also allow the Division to assess the effectiveness of zebrafish for future toxicity assessments of other heavy metals. Using zebrafish may allow researchers to perform toxicities faster and at a lower cost. Preliminary findings from this work were presented at governmental workshops in 2021.

Anesthesia-Related Neurotoxicity

The Division has been a leader in the field of developmental anesthesia-related neurotoxicity for over a decade. It is continuing this rich tradition by performing formal toxicity assessments, working to understand the conditions that lead to toxicity, and describing the mechanisms of toxicity. In collaboration with CDER, DNT scientists completed the experimental phase of an assessment of the neurotoxic potential of ketamine in a pediatric population. Moreover, the Division is using alternative assays to study the comparative toxicity of different anesthetic regimens and will soon begin studies to assess the interactions between cannabinoids and opioids on brain development. Through this work, the Division's goal is to understand the conditions needed for anesthesia-related neurotoxicity and to better define the risk associated with general anesthesia in a pediatric population.

Select 2021 DNT Publications

- *Effect of Ketamine on Gene Expression in Zebrafish Embryos*
- *Evaluation of Styrylbenzene Analog- FSB and its Affinity to Bind Parenchymal Plaques and Tangles in Patients of Alzheimer's Disease*
- *Neurobehavioral and Neurochemical Effects of Perinatal Arsenite Exposure in Sprague-Dawley Rats*
- *Sexually Dimorphic Associations Between Prenatal Blood Lead Exposure and Performance on a Behavioral Testing Battery in Children*

DNT Events in 2021

NCTR Seminar Series Roundtable Discussion with Students from UAMS, November 2021

NCTR's Division of Neurotoxicology hosted a virtual roundtable discussion for Systems Pharmacology and Toxicology (SPaT) students from the University of Arkansas for Medical Sciences (UAMS). The SPaT program is designed for Ph.D. students pursuing dissertation research projects in the pharmacological sciences. The program trains students to use an in-vivo approach to answering relevant questions in pharmacology and toxicology. This type of training provides students with a much broader perspective on pharmacology and toxicology that better prepares them to be leaders of multi-disciplinary research teams in the pharmacological sciences.

Division of Systems Biology

About the Division

The Division of Systems Biology (DSB) focuses on the development and evaluation of new technologies and the identification of new biomarkers — indicators of disease — to support the FDA's mission. The Division's mission is to address problems of food, drug, and medical-product safety using systems-biology approaches and innovative technology.

Overview of DSB Research

In 2021, the Division continued existing projects and began new projects covering a broad range of scientific topics designed to contribute to the NCTR and FDA missions. Despite the ongoing pandemic and associated limitations related to the number of on-site staff and supply deliveries, DSB scientists published 18 research articles, presented at 12 national and international scientific conferences, provided consults to and collaborated with FDA product centers, supported projects led by other NCTR research divisions, and initiated 9 studies to address COVID-19 knowledge gaps. Other DSB accomplishments for 2021 include expanding and strengthening internal FDA and external collaborations, acquiring funds external to the Division for projects (e.g., intramural awards, CDER, COVID, etc.), team building, and research resources (e.g., instrumentation and access to specialty facilities necessary for conducting the studies).

Working Groups

DSB scientists made significant contributions in 2021 to NCTR working groups, FDA working groups (e.g., Biomarkers, Omics, COVID-19, Toxicology, Alternative Methods), and FDA product center-led working groups (e.g., Oligonucleotides, Neurotoxicity Assessment, Pharmacokinetics and Toxicokinetics). In addition, many DSB scientists presented oral talks and posters, co-chaired, and/or served on committees for external scientific conferences and organizations, such as Health and Environmental Sciences Institute and Organisation for Economic Co-operation and Development.

Project Funding Awards

DSB received the following funding awards in 2021:

- FY21 funding for 8 projects.
- FY22 funding for 4 projects.
- Both FY21 and FY22 funding for 6 projects.
- External funding for 5 projects.

COVID-19 Response

- DSB — with the help of NCTR Center leadership — recruited funding for two Broad Agency Announcement (BAA) contracts that enable NCTR scientists to 1) conduct Biosafety Level 3 studies with SARS-CoV-2 viral strains at the Regional Biocontainment Laboratory at the University of Tennessee Health Science Center (USTHSC), and 2) correlate Matrix- Assisted Laser Desorption-Ionization (MALDI)-imaging mass spectrometry data from COVID-19 infections (human and animal models) with high-powered broadband coherent anti-stokes Raman scattering (BCARS) imaging technologies at Georgia Tech. Research data resulting from these BAA contracts with

UTHSC and Georgia Tech are expected to make significant impacts in scientific areas related to:

  - SARS-CoV-2 infection
  - Host-immune responses
  - Therapeutic combinations
  - Perinatal risks
  - Disease pathogenesis
  - Therapeutic risks
  - Variant cross-reactivity of vaccine targets
  - Potential biomarkers

- Scientists within DSB and NCTR's Bioinformatics and Biostatistics collaborated in using homology modeling computational chemistry to identify key interactions between the SARS-CoV-2 infection co-receptor angiotensin converting enzyme 2 and the full-length spike protein trimer of SARS-CoV-2. *Frontiers in Chemistry*.

Ongoing Research Projects

As a result of outreach efforts, several project proposals were initiated and/or planned for development in 2022, including studies in the following topics:

- COVID-19
- Vaccines
- Cannabinoids
- Cystic fibrosis transmembrane conductance regulator (CFTR) modulators

In addition, opportunities for new collaborations with academia and access to clinical samples, such as multisystem inflammatory syndrome in children (MIS-C) pediatric samples, were also initiated, which will complement ongoing studies and create opportunities for new projects that will contribute to the NCTR and FDA missions.

Office of Scientific Coordination

About the Office

The 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

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 following ensure the high quality of studies at NCTR: 1) verification of test-article identity and purity, 2) certification of concentration and stability of test articles in dosing solutions and vehicles, and 3) surveillance of animal study materials (bedding, water, and diet) performed routinely.

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, formulation and administration of test articles, sample collection, and data collection. The contractor works with the veterinary staff and Institutional Animal Care and Use Committee (IACUC) to ensure the health and welfare of the animals.

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.

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.

Microbiology Surveillance Laboratory

The Microbiology Surveillance Laboratory staff ensures the research animals, environment, 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. The staff provides accurate and timely identification and characterization of microbes using advanced technologies including biochemical metabolism, MALDI-TOF mass spectrometry, and next-generation sequencing. The laboratory staff also supports other microbiology-related research studies from all NCTR research divisions.

Nanotechnology

The NCTR/ORA Nanotechnology Core Facility (NanoCore) supports collaborative nanotechnology research within FDA and research between FDA and other government

agencies and universities. This facility is well-equipped with advanced analytical equipment, including electron, atomic force and optical microscopy, scattering, diffraction, spectroscopy, fractionation, chromatography, and elemental analysis facilities for nanomaterial assessment. Apart from these, laboratories are equipped for in vitro and in vivo biological studies. NanoCore research provides information on nanomaterial characterization and the safety of products containing nanomaterials in FDA-regulated products. This research data is also used in staff and reviewer training and in establishing standards for use by stakeholders developing nanotechnology products. Nanomaterials can have different chemical, physical, or biological properties than their conventionally scaled counterpart materials that are used in many products regulated by FDA. To date, over 970 drug products that contain nanomaterials have been submitted to FDA, with over 70 products approved for clinical use, highlighting the importance of this line of research.

Pathology Services Contract

NCTR maintains an on-site pathology contract for veterinary pathology and histopathology services. Three veterinary pathologists and a highly trained staff provide NCTR with services including clinical pathology, histopathology slide preparation, rigorous pathology examination, and complete histopathology and pathology reports.

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

Select OSC Accomplishments in 2021

- **Veterinary Services** supported 38 in vivo studies and maintained high standards of animal care including compliance with OLAW regulations and AAALAC standards during the ongoing COVID-19 pandemic.
- In a joint effort between **OSC Experimental Support Liaisons**, DBB's Scientific Computing Branch, OIMT, DBT, **OSC Veterinary Services,** and on-site contractors (**Toxicologic Pathology Associates** and **Bionetics**), user acceptance tests were successfully completed for a new data collection and management system. Phases 2 and 3 of validation are ongoing.
- In support of CTP-sponsored studies with NCTR's DBT, the **OSC Analytical Chemistry Unit** completed the analysis of bioanalytical samples (plasma, urine, and tissues) associated with a single-dose study to investigate the pharmacokinetics of nicotine after oral, intravenous, and inhalation exposure. The unit also completed bioanalytical work on an inhalation study to examine the transition from a propylene glycol-based formulation for nicotine to a saline-based formulation.
- The **OSC Analytical Chemistry Unit** developed analytical methodology and completed the analysis of cannabidiol (CBD) and two of its major oxidative metabolites in rat plasma and brain for a DNT study.

- The **OSC Analytical Chemistry Unit** established analytical methodology to screen lorcaserin test-article materials for a potentially genotoxic nitrosamine contaminant in a collaboration for a DGMT study.
- The **OSC Analytical Chemistry Unit** collaborated on a DSB project to evaluate an in vitro model of the human placental barrier model using test compounds such as rifaximin, glyburide, caffeine and fentanyl. Sensitive analytical methods were developed to analyze the same compounds in rat plasma, placenta, and fetal tissues to correlate with the in vitro work.
- The **Microbiology Surveillance Unit** supported the animal facility surveillance program by:
    - Screening the breeding colony, sentinel animals and quarantine animals for pathogenic microorganisms including bacteria, viruses, and parasites.
    - Analyzing 3,262 swab samples from rooms, cages and equipment; 664 feed and water samples; and 576 cage water bottles to ensure the animal facility remains pathogen-free.
    - Developing a new diagnostic method based on 16s rRNA sequencing and is undergoing staff training.
- The **Microiology Survelliance Unit** published two papers about this research in collaboration with NCTR research divisions, including DM. *Microbiol. Res. Announce*. (October 2021 and November 2021)

Summer Student Research Program

Each summer for over 30 years, NCTR has provided undergraduates, entering graduate students, or graduate students the opportunity to work with NCTR principal investigators, preparing countless students for career success.

The 2021 Summer Student Research Program (SSRP) ran from June 1 through August 6, 2021, and hosted 29 students — 21 undergraduate students and 8 graduate students. The program participants were from diverse areas across the U.S. and conducted research in all NCTR divisions and at ARKL/ ORA.

During the ten-week program participants learned laboratory skills, attended the Lunch-and-Learn series organized by Dr. Si Chen and Dr. Volodymyr Tryndyak, and gave oral presentations. NCTR submitted 20 posters to the annual FDA Summer Student Science Poster Day in August.

- NCTR's 2021 program was organized by the SSRP committee led by Page McKinzie and Laura Schnackenberg, SSRP 2021 Committee co-chairs.
- 29 SSRP participants came from diverse areas across the U.S.:
  - Arkansas – 7
  - California – 2
  - Florida – 1
  - Illinois – 3
  - North Carolina – 1
  - Michigan – 1
  - Mississippi – 1
  - New Jersey – 4
  - New York – 3
  - Tennessee – 2
  - Texas – 3
- Number of SSRP participants per division/office:
  - DBT – 4
  - DBB – 6
  - DGMT – 3
  - DSB – 2
  - Microbiology – 9
  - Neurotoxicology – 2
  - ORA – 1
  - OSC – 2

In Memory – Dr. Carl Cerniglia

Carl Cerniglia, Ph.D.
Director, Division of Microbiology
(1948 - 2021)

On April 9, 2021, NCTR and the FDA community unexpectedly lost a dear friend and colleague, Dr. Carl Cerniglia. He was a mentor to many, enjoyed sports and travel, and was a passionate runner who completed numerous marathons. He had a scientific career that made a global impact – improving our health, safety, and environment. Since 1980, Carl served as the Director of the Division of Microbiology at NCTR and as a member of the Senior Biomedical Research Service for the FDA, a job he deeply loved, leading a group of dedicated, world-renowned professionals.

Dr. Cerniglia's research resulted in over 400 technical publications, 39 book chapters, and numerous review articles. He co-edited a book on "Microbial Transformation and Degradation of Toxic Organic Chemicals." His research was frequently highlighted in the scientific and popular press. Dr. Cerniglia gave more than 400 invited presentations at national and international conferences and meetings and was also an American Society for Microbiology lecturer.

Dr. Cerniglia's research achievements were recognized by national and international awards from:

- American Academy of Microbiology
- American Pharmaceutical Association
- American Society for Microbiology
- Department of Health and Human Services
- Food and Drug Administration
- International Society of Toxicity Testing

Dr. Cerniglia's awards included:

- WHO Silver Medal Award
- FDA Award Merit
- HHS Outstanding Leader Award
- Distinguished Alumnus Award, North Carolina State University

NCTR held its inaugural "Carl Cerniglia 5K Run/Walk" on May 3, 2021, during Public Service Recognition Week in celebration of Carl's life and his 40-plus years of public service.

"Carl was a consummate runner and researcher; he encouraged us to get in shape and finish strong."

Dr. William Slikker, Jr.
NCTR Center Director

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