U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research (NCTR)

Genetic & Molecular Toxicology

About the Division of Genetic & Molecular Toxicology (DGMT)

Division Mission

Develop and validate genetic toxicity assays and interpret genetic toxicity findings for regulatory decision-making.

Goals

- Respond to Agency needs for expertise and chemical-specific data (*e.g.*, nanomaterials, tobacco products, drug impurities).
- Maintain DGMT's tradition of leadership in regulatory assay development and validation (*e.g.*, MLA, *Hprt*, MN, TGR, miniAmes, *Pig-a*, in vitro organotypic models).
- Develop better methods for carcinogenicity testing and translation of rodent studies to human risk (*e.g.*, CarcSeq).
- Develop advanced in vitro toxicological models that incorporate genotoxicity endpoints (*e.g.*, human ALI airway model).

Research Strategies

- Engage FDA product centers, National Toxicology Program, and other national and international organizations to set research priorities.
- Develop better biological models for assessing human risk (e.g., airway and testes organotypic in-vitro models, liver spheroids).
- Develop more comprehensive approaches for monitoring genetic variation: error-corrected/error-avoidance next generation sequencing (ec/eaNGS).

Select DGMT Accomplishments in 2021

Guidelines for Conducting Rodent Erythrocyte *Pig*-a Assay

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

Mutation Analysis Using Error-Corrected Next Generation Sequencing

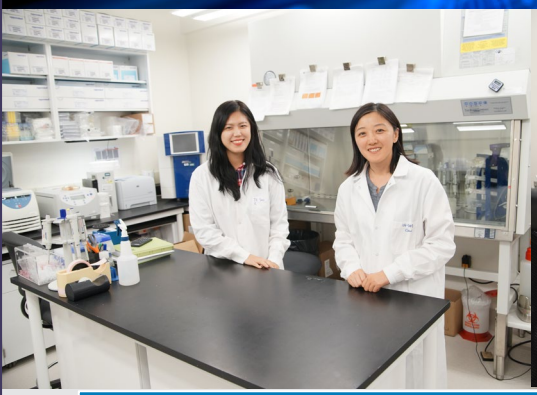
Error-corrected next generation sequencing (ec-NGS) is a potentially powerful approach for evaluating rare mutations directly by the changes they make in the DNA sequence of the genome. Mutation is used by the FDA in safety evaluations of regulated products as a biomarker of carcinogenicity. DGMT scientists successfully conducted ec-NGS analyses in bacteria, *C. elegans*, and mammalian cells, including the cells from an organotypic tissue model, using two platforms — Duplex Sequencing and PacBio HiFi Sequencing.

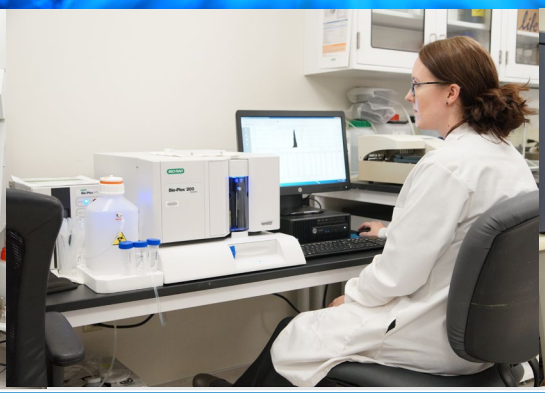
NCTR Division of Genetic and Molecular Toxicology
Robert H. Heflich, Ph.D., Division Director
Jefferson, AR
www.fda.gov/NCTR

U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research (NCTR)

Genetic & Molecular Toxicology





Ongoing DGMT Research Projects in 2022

- High-Content High-Throughput Genetic Toxicology Evaluations Using Metabolically Active Hepatic Cell Lines and Primary Hepatic Cells from Humans
- Genetic Toxicology Analysis Using a Panel of 14 Human Cell Lines, Each Expressing a Different Human Drug Metabolizing Enzyme
- Mutagenicity Evaluations of Drug Impurities in Support of the Center for Drug Evaluation and Research Nitrosamine Drug Impurity Task Force
- A Validation Study of Vitrocell Exposure Systems to Investigate the In Vitro Toxicity of Electronic Nicotine Delivery Systems at the Air-Liquid Interface of Human Airway Tissue Models
- Developing an In Vitro System to Evaluate the Disease-Related Toxic Effects of Inhaled Aerosols and Vapors in Human Airway Tissue Models
- Development of an In Vitro Co-Culture System to Test the Adverse Effects of Drugs and Their Metabolites on Human Embryo-Fetal Development
- Development of a Microphysiological System for Evaluating Zika Virus Sexual Transmission Using a Testicular Model
- Development of a Microphysiological System for Evaluating Antibody Therapies Targeting Viral Infections During Pregnancy: a Zika Virus Case Study

NCTR Division of Genetic and Molecular Toxicology
Robert H. Heflich, Ph.D., Division Director
Jefferson, AR
www.fda.gov/NCTR