Division of Microbiology

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Division Director

Views expressed in this presentation are those of the presenter and not necessarily those of the U.S. Food and Drug Administration

Division of Microbiology

Mission

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.

Vision

Strive to be a valued resource in advancing regulatory science research in microbiology for FDA.

Meeting the Division Mission and Vision

Contribute to FDA Guidelines & Regulations

- Understand the regulatory process in order to identify issues
- Integrate research program into the FDA infrastructure
- Contribute to NCTR/FDA mission

Enhance FDA Research Interactions

- Assess the needs of FDA
- Conduct research critical to the FDA regulatory science mission
- Expand our collaborative relationship with FDA Centers & ORA

Strengthen Research Program Management

- Focus research priorities in consultation with regulatory colleagues
- Establish benchmarks of scientific excellence
- Communicate research in plain language
- Upgrade research facilities and infrastructure

Division Staff

- **Government Positions** —28 Full time employees (FTEs)
  - Research Scientists & Staff Fellows: 19 FTE
  - Support Scientists : 4 FTE
  - Administrative : 4 FTE
  - FDA Commissioner Fellows: 1 FTE
- **ORISE Post Docs, Graduate Students, etc.:** 10 staff members
- **Visiting Scientists:** 2 staff members
- **Total** = 40 staff members

Outreach

- Collaborations with:
  - All FDA Centers and NCTR Research Divisions
  - National Toxicology Program
  - USDA, CDC, Arkansas Health Department
  - Universities: Local, National and International
- Global/National Outreach:
  - WHO Committees: JECFA (food additives), JMPR (pesticide residues)
  - Science Advisory Boards
  - Journal Editorial Boards
  - U.S. Government Panels: USDA, EPA, NOAA, Microbiome Interagency Working Group
  - Visiting Scientist Programs
  - FDA-wide Expert Committees, Working groups from FDA Centers

Microbiology Research Areas

- Evaluating interactions between microbiome, antimicrobial agents, food contaminants, food additives, food supplements and FDA-regulated products
- Developing methods to detect and characterize foodborne and other pathogens
- Determining antimicrobial resistance and virulence mechanisms of pathogens
- Improving risk assessments of priority pollutants, including polycyclic aromatic hydrocarbons and drugs, by integrating systems biology approaches
- Conducting research to aid FDA in the areas of women's health, tobacco products, and nanotechnology

Three Top Accomplishments

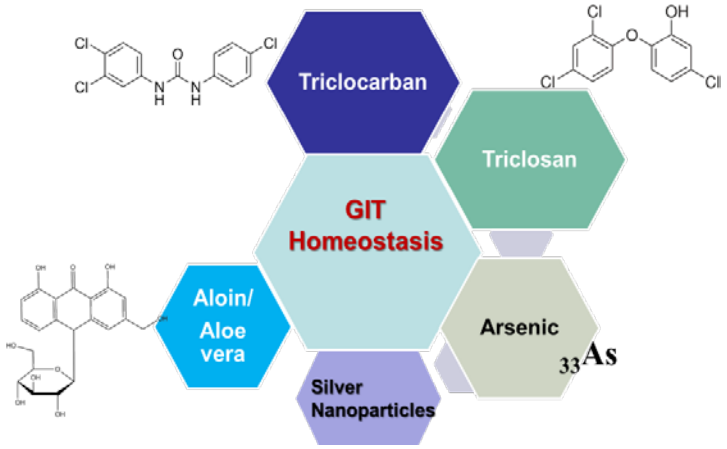
1. Conducting host-microbiome assessments to evaluate the impact of xenobiotic compounds on the gastrointestinal microbiome and immune response and to establish a standardized approach within the NTP program for risk assessments (NTP)

2. Development of methods to detect and characterize *Burkholderia cepacia* complex in pharmaceutical products (CDER)

3. Determination of the microbial populations within smokeless tobacco products and assess the impact on the formation of tobacco specific nitrosamines (CTP)

Capability-Building for Microbiome Assessment in Toxicology Studies

- Studies addressing critical knowledge gaps in toxicity testing risk assessments
  - Acute and/or chronic exposure to test compounds are being studied in experimental models to translate results to human exposure
- Conducting host-microbiome assessments to evaluate the impact on the gastrointestinal microbiome and immune response and to establish a standardized approach within the NTP program
  - sample collection and methodologies for gastrointestinal microbiome analysis
  - standardized data analysis and approaches for data-repository and data presentation



U.S. FOOD & DRUG ADMINISTRATION
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

National Toxicology Program
U.S. Department of Health and Human Services

Developing Methods To Detect and Characterize Pathogens

- *Burkholderia cepacia* has been associated with outbreaks as a microbial contaminant in pharmaceutical products
  - Methods have been developed to increase the ability to detect and culture *B. cepacia*

- Providing data on the susceptibility, survival and detection of *Burkholderia* in products containing antiseptics and the importance of proper antiseptic concentrations in pharmaceutical products

National Center for Toxicological Research ⟷ **COLLABORATION** ⟷ **Center for Drug Evaluation and Research**

Microbial Populations Within Smokeless Tobacco Products

- Data on the microbial population in smokeless tobacco products (STPs) has been limited
  - Bacterial species identified in certain STPs may act as opportunistic pathogens
  - Some species are known to reduce nitrate, which may provide precursors for the formation of carcinogenic tobacco-specific nitrosamines (TSNAs)

- Continuing studies are examining the potential contributions of microorganisms in STPs to TSNA formation

Additional Representative Projects

1. Evaluation of potential antimicrobial resistance selection in human intestinal microbiota following long-term exposure to residual concentrations of antimicrobial drugs (CVM)
2. Evaluate the plasmid-associated antimicrobial resistance and virulence in *Salmonella* (CVM)
3. Evaluate the effect of nanoparticles and nanodrugs on the intestinal microbiota and immune function (NanoCore, CDER)
4. Detection of microbial contaminants, including pathogenic mycobacteria, in tattoo inks (CFSAN)
5. Exploration of fecal transplant mechanisms: Differential pro-inflammatory responses of intestinal epithelial and dendritic cells to *Clostridium difficile* and commensal bacteria (CBER)
6. Evaluate molecular assays and culture-based reference methods for the detection of toxigenic *C. difficile* (CDRH)
7. Development of in vitro vaginal tract models to assess the probiotic potential of naturally-occurring *Lactobacillus* strains toward toxic shock syndrome toxin-1 producing strains of *S. aureus* (OWH)

Impact of Antimicrobial Residues on the Gastrointestinal (GI) Microbiota

- Evaluating whether the ingestion of antimicrobial agents at residues levels concentrations impact the human GI tract microbiota
  - Are there shifts in the microbiota populations?
  - Is there selection of antimicrobial-resistant bacteria?
  - Do GI bacteria degrade or inactivate the drug?
- Earlier studies on fluoroquinolones supported VICH GL #36: "Studies to Evaluate the Safety of Residue of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI"
- New studies are being conducted to evaluate the impact of tetracycline and erythromycin on the GI microbiota

Plasmid-Associated Antimicrobial Resistance and Virulence in *Salmonella*

- DNA sequence analysis and *in vitro* assessment to characterize virulence in antimicrobial resistant strains

- Plasmids allow for the potential transfer of antimicrobial resistance and virulence-associated genes among bacterial
  - Antimicrobial exposure appears to impact plasmid transfer dynamics in a number of cases
  - Transmissible plasmids can contain both resistance and virulence genes

- Ongoing studies are evaluating the contribution of the plasmid-encoded to increased virulence and colonization ability
  - Important to understand to evaluate risks of antimicrobial use

Nanoparticles and the Impact on the Microbiota and Immune Response

- Examination of the impact of selected nanoparticles on representative bacterial populations of the GI tract
  - *In vitro* and *in vivo* animal studies
- Determination of the impact of nanoparticles on the permeability intestinal epithelial barrier
- Delineation of the interaction of nanoparticles at the gastrointestinal surface with the gut-associated immune responses.
- Evaluation of the expression of genes involved in the host innate immune response (proinflammatory and anti-inflammatory genes)

Detection of Microbial Contaminants in Tattoo Inks

- Approximately 25% of 18-50 year olds in the U.S. have at least one tattoo
- Multiple recent reports of outbreaks by pathogenic Mycobacteria following tattooing
  - Tattoo inks were found to be contaminated with *Mycobacteria chelonae* and related species
- Current project involves assaying tattoo inks previously used at the NCTR in toxicology testing and those requested by CFSAN for microbial contamination.
- Development culture based and molecular methods for rapid detection and monitoring of pathogenic mycobacteria, including *M. chelonae*, in tattoo inks

Evaluation of *Lactobacillus* Inhibition of Toxic Shock Syndrome Toxin-1 Producing Strains of *S. aureus*

- Development of *in vitro* vaginal tract models to assess the probiotic potential of naturally-occurring *Lactobacillus* strains toward toxic shock syndrome toxin-1 (TSST-1) producing strains of *S. aureus*
  - Developed a defined medium that simulates vaginal secretions and supports the growth of *Lactobacillus* species and clinical strains o*f S. aureus*
    - Lysostaphin-producing *L. plantarum* WCFS1 strain being evaluated for probiotic potential
- *Staphylococcus aureus* and the production of TSST-1 as influenced by tampons
  - Characterizing the TSST-1 and alpha-toxin producing capabilities of clinical strains from menstrual toxic shock syndrome

Reference Methods for the Detection of Toxigenic *C. difficile*

- Evaluation of molecular assays and culture-based reference methods for the detection of toxigenic *C. difficile*
  - Development of a composite molecular method for the detection of *C. difficile* in human stool samples
  - Comparison of the composite molecular method to the currently accepted reference method toxigenic culture and to an FDA-cleared nucleic acid test, for the detection of toxigenic *C. difficile*
  - Evaluation of the effects of storage conditions on viability of *C. difficile* vegetative cells and spores in clinical stool specimens

Exploration of Immune Response Following Fecal Transplant

- Develop an increased understanding of how commensal intestinal bacteria modulate pro-inflammatory signaling responses to *Clostridium difficile* infection
  - Provide insight for regulation of fecal microbiota transplantation and options for alternative therapies
- Establish a cell-culture model to evaluate the immune response of following microbial challenge with *C. difficile* and representative commensal bacteria
  - Characterization of microbial modulation of host responses and identification of specific cellular responses associated with morbidity and mortality of *C. difficile* disease

Future Direction of the Division

Strategies:

- Increase the capacity and resources to conduct research to better understand the impact of FDA-regulated products on the microbiome and conversely, the impact of the microbiome on FDA-regulated products
- Advance new scientific approaches to determine the impact of chemical and microbial contaminants in foods and other FDA regulated products on the human microbiome
- Improve toxicology and environmental risk safety assessments of human and veterinary drugs and priority pollutants through the integration of systems biology approaches

Future Direction of the Division

- Continue to work with CTP to advance their research priorities to provide data directly relevant to their mission on the regulation of tobacco products
- Continue to develop nanotechnology projects in collaboration with the NCTR/ORA NanoCore Facility and FDA regulatory centers
- Build on previously funded studies in women's health to identify research gaps to address new initiatives with the Office of Women's Health
- Identify opportunities to leverage opportunities with other federal, state and international regulatory and public health agencies, academia and industry

Future Direction of the Division

- The Division is diverse in expertise and well suited to meet the microbiological needs of FDA Centers and special programs (OWH, OCS, etc.)
  - Therefore we are working to reach out to our stakeholders to develop research projects that help them address their needs to meet FDA's mission
- Through these interactions with the FDA Centers, we have prioritized our research efforts by moving away from areas of with less need to those more pressing to the agency
  - This flexibility is an key asset to the NCTR and FDA as a whole

Feedback Requested

- As a Division, are we addressing the needs of the FDA Centers?
  - What emerging sciences/technologies can you advise the Division to pursue?
    - More work in the microbiome area as it relates to regulatory science?
- How can we do a better job of engaging the Centers to learn about the needs?
- What future directions do you recommend for this Division that would impact the FDA?

Thanks

- Members of the Science Advisory Board
- Representatives of FDA Centers and Offices
- Dr. William Slikker. Jr., Director, NCTR
- Dr. Daniel Acosta, Deputy Director, NCTR
- Dr. Donna Mendrick, Assoc. Director for Regulatory Activities
- Division of Microbiology Staff

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