Center for Biologics Evaluation and Research

Research informing tomorrow's biologics

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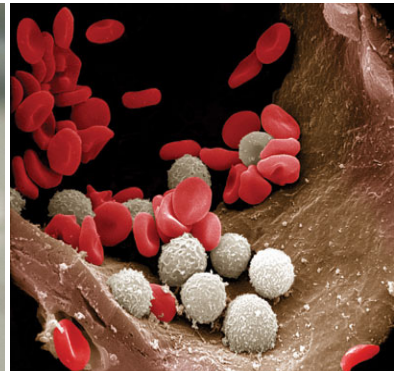
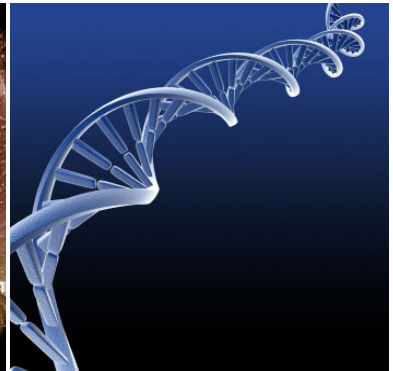
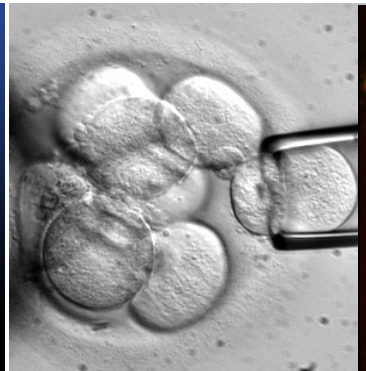
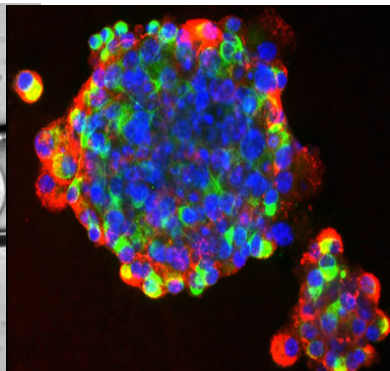
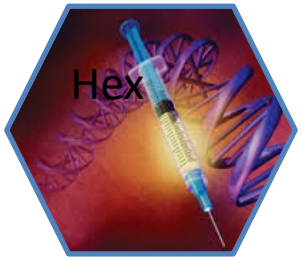
Associate Director for Research

CBER. U.S. Food and Drug Administration

Products Regulated by CBER

- Allergenics
- Blood and Blood Components
- Blood Derivatives
- Devices Related to Biologics
- Gene Therapies
- Human Tissues and Cellular Products
- Vaccines (preventative and therapeutic)
- Live Biotherapeutic Products
- Xenotransplantation Products



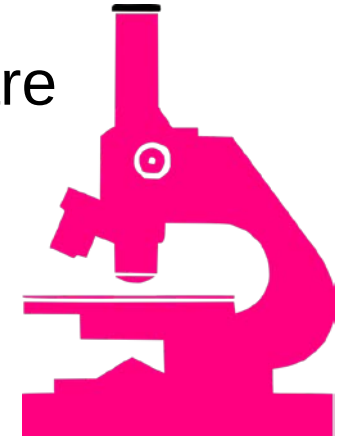
CBER Research Goals

Advancing the scientific basis for regulation of biologics, human tissues and blood by:

- **Goal 1** — Developing and evaluating technology, reagents, and standards to inform and improve chemistry, manufacturing, and controls (CMC).
- **Goal 2** — Developing and assessing nonclinical models and methods predictive of clinical performance with respect to toxicity and effectiveness.
- **Goal 3** — Improving clinical evaluation pre- and post-licensure through use of big data, innovative designs and statistical, analytical and modeling approaches.
- **Goal 4** — Preparing for future regulatory and public health challenges.

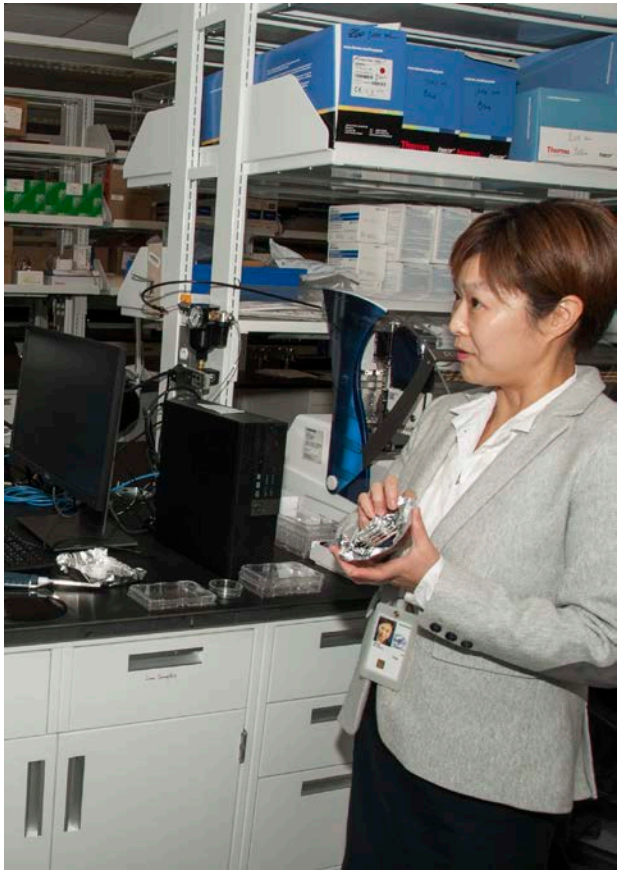
Scientific Expertise

- Applied technologies: NMR, mass spec, flow cytometry, microarray, high throughput sequencing and related bioinformatics/IT
- Microbiology: parasitology, bacteriology, virology, microbiome
- Immunology
- Biochemistry and molecular biology
- Cell and developmental biology, tissue engineering, and microphysiologic systems
- Epidemiology, meta-analyses of large healthcare databases
- Biostatistics
- Bioinformatics



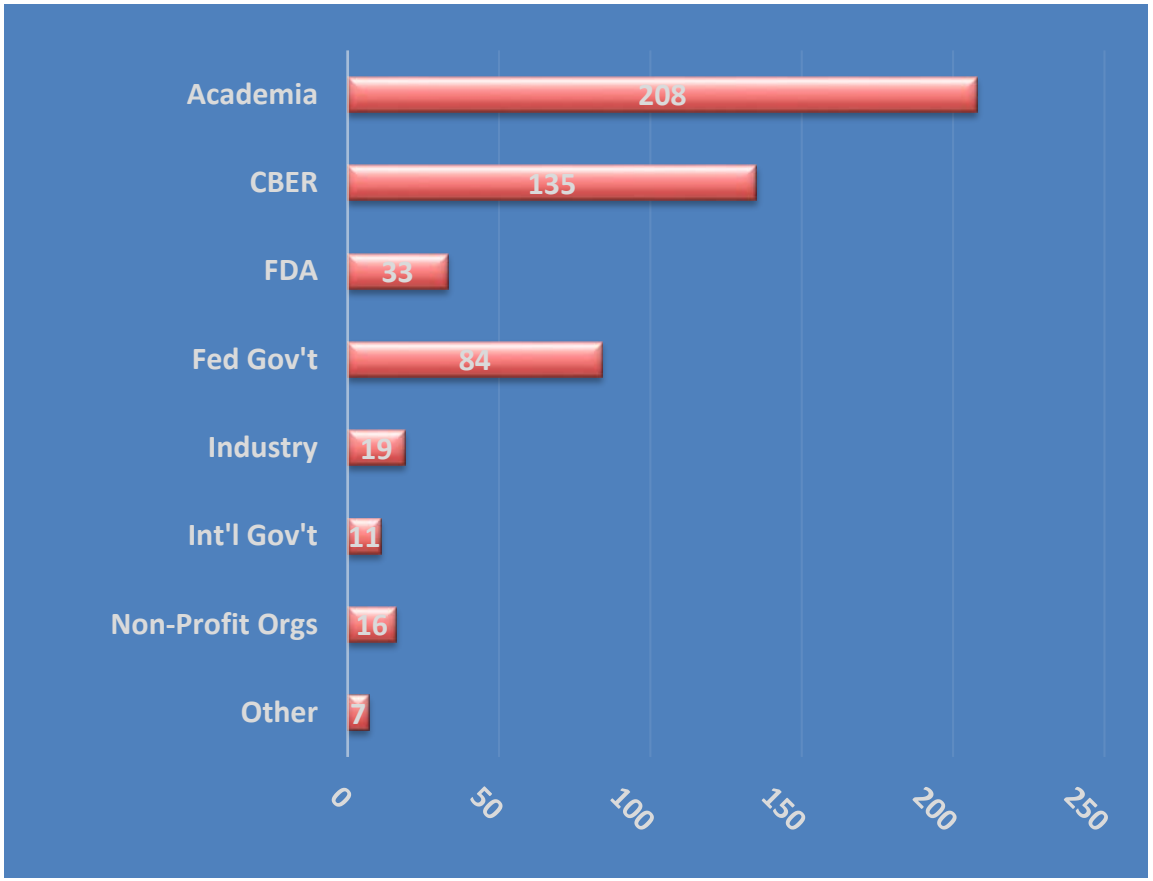
White Oak Lab Facility

- Core Facilities:
  - Flow cytometry
  - Confocal and electron microscopy
  - Biotechnology
    - ✓ Illumina HiSeq and MiSeq
    - ✓ Oligonucleotide, siRNA, PNA, and peptide synthesis
    - ✓ Peptide and DNA sequencing (ABI, capillary)
    - ✓ Taqman probe synthesis
    - ✓ HPLC; Capillary electrophoresis
    - ✓ Mass Spectrometry/Proteomics
    - ✓ Amino acid analysis
  - Bioinformatics support for NGS data analysis and storage



- State-of-the-Art Vivarium
  - Imaging facility with MRI, digital X-ray, IVIS, ultrasound, CT
  - ABSL-2 and -3; procedure rooms
  - Transgenic derivation facility

CBER Advances Regulatory Science through External Collaborations



33 ongoing collaborations non-CBER, FDA scientists

9 of these are with NCTR scientists:

- **5 leveraging NCTR to support CBER**
- 4 leveraging CBER to support NCTR

Data from FY19 CBER Research Reporting Database

CBER-relevant NCTR Collaborations

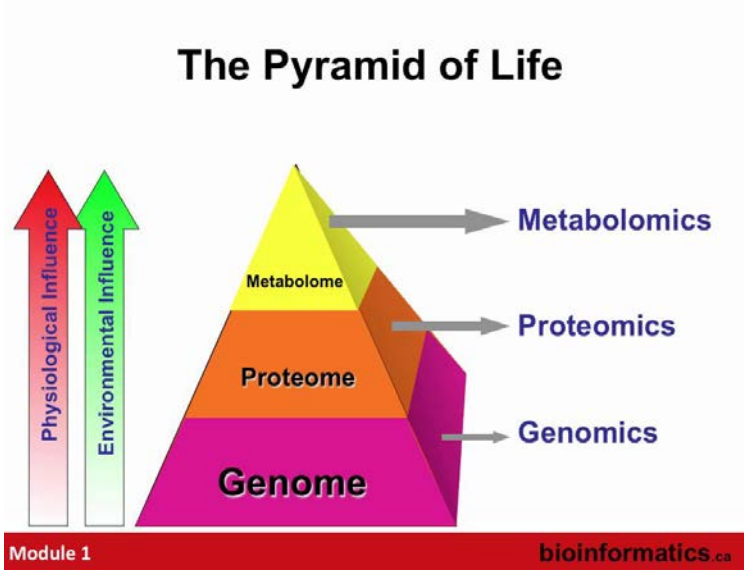
- Goal 1: CMC
  - Detect off-target mutations of gene editing (CBER Goal 2 as well): ONGOING

Detect off-target mutations of gene editing

- *Collaborators*: Javier Revello (NCTR); Zhaohui Ye (CBER)
- *Need*: New sensitive methods to detect and provide functional evaluation of unintended mutations in human gene therapeutic products using genome editing technologies.
- *Why NCTR*: Experience in genotoxicity and NGS
- *Impact*: The outcome of this study will help address a significant regulatory challenge in evaluating the safety of genome editing technologies as they apply to the development of advanced therapies.

CBER-relevant NCTR Collaborations
Goal 2: Nonclinical

- *B. pertussis* and ALI model
- Metabolomic analyses on fecal samples
- Lipodomics analyses on macrophage incubated with sera
- Improving understanding of norovirus diversity to inform vaccine design
  - Ford-Siltz, LA; Mullis, L; Sanad, YM; Tohma, K; Lepore, CJ; Avezedo, M; Parra, GI. Genomics analyses of GIV and GVI noroviruses reveal the distinct clustering of human and animal viruses. Viruses. 2019. 11(3). doi: 10.3390/v11030204.



Bordetella pertussis adhesion and pathogenesis in an in vitro human airway epithelial tissue model

- *Collaborators:*
  - NCTR: Rui Xiong, Xuefei Cao, Yiying Wang, Roberta Mittelstaedt, Jin Hann and Robert Heflich
  - CBER: Tod Merkel, Kelsey Gregg
- *Need:*
  - In vitro preclinical model for studying *B. pertussis* pathogenesis; evaluate vaccine efficacy
  - Address need for correlates of protection and clearance for *B. pertussis*
- *Why NCTR:*
  - Expertise in air-liquid-interface human airway tissue model
- *Impact:*
  - AI model may provide mechanistic evidence to support regulatory review of vaccines
  - Study may support use of ALI model for preclinical assessment of vaccines against other respiratory pathogens

Metabolomic analyses on fecal samples: Detection of cefaperazone in mice

Collaborators: Jinchun Sun (NCTR) and Paul Carlson (CBER)

Need: Demonstrate differences of mouse *C. difficile* model were not due to changes in antibiotic breakdown.

Why NCTR: NCTR's expertise in global metabolomics; ability to develop quantitative assay

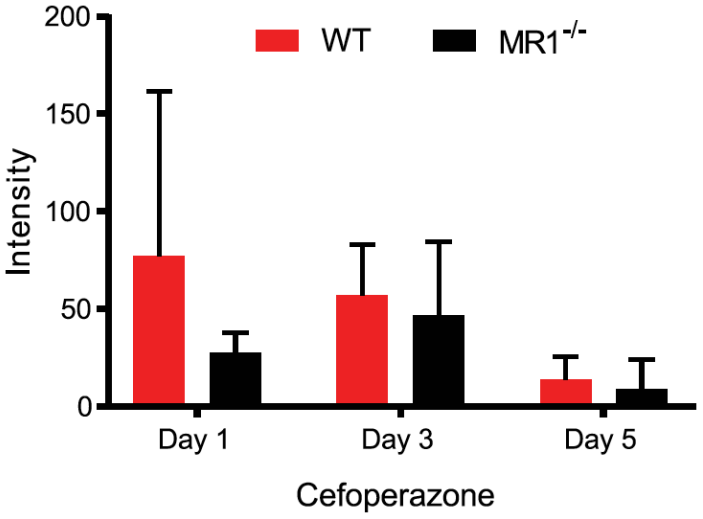
Impact: Required for publication – important new animal model may provide means to study FMT effectiveness in treating/preventing *C. difficile*

RESEARCH ARTICLE

Microbiota of MR1 deficient mice confer resistance against *Clostridium difficile* infection

Ashley D. Smith[1], Elissa D. Foss[1], Irma Zhang[1], Jessica L. Hastie[1], Nicole P. Giordano[1], Lusine Gasparyan[2], Lam Phuc VinhNguyen[2], Alyxandria M. Schubert[1], Deepika Prasad[1,2], Hannah L. McMichael[1], Jinchun Sun[3], Richard D. Beger[3], Vahan Simonyan[2], Siobhán C. Cowley[1], Paul E. Carlson, Jr[1]*

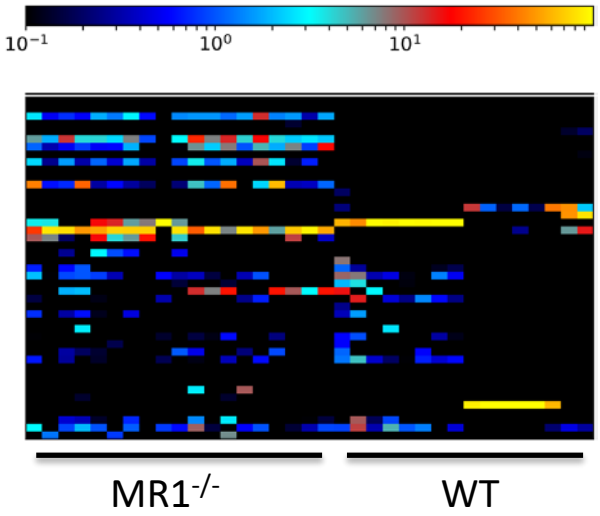
1 Laboratory of Mucosal Pathogens and Cellular Immunology, Division of Bacterial Pathogens and Allergenic Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, United States Food and Drug Administration, Silver Spring, Maryland, United States of America, **2** High-performance Integrated Personal Environment, Center for Biologics Evaluation and Research, United States Food and Drug Administration, Silver Spring, Maryland, United States of America, **3** Division of Systems Biology, National Center for Toxicological Research, United States Food and Drug Administration, Jefferson, Arkansas, United States of America



Next steps: Combining metagenomic and metabolomic data to identify microbiome-specific <u>mechanisms</u> of CDI resistance

- Identification of functional pathways and products in a combination of metagenomic (CBER) and metabolomic (NCTR) data can help identify targets worth pursuing in large data sets.

- Example:
  - Pathway for 4-hydroxybenzoate biosynthesis (PWY-6435) identified in all metagenomes of all KO mice and none of the WT mice.
  - Hydroxybenzoate also found in metabolomic data from KO mice.
  - This antioxidant is currently used as a food preservative (Parabens).
  - **<u>Does this compound inhibit *C. difficile* growth?</u>**

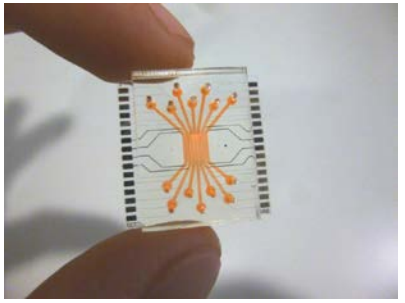


Lipodomics analyses on macrophage incubated with sera – mechanistic insights into vaccines and neonates

- *Collaborators*: Jinchun Sun(NCTR);
  Mustafa Akkoyunlu(CBER)
- *Need*: Lipodomics analysis of sera and cells incubated with sera to explore a hypothesis about unresponsiveness of neonates to certain vaccines
- *Why NCTR*: Expertise in lipodomics
- *Impact*: The outcome of this study may provide new insights into the immunomodulatory properties of sera on immune cells. May inform development of effective vaccines.

Other CBER-NCTR Collaborations

- Exploration of a microfluidic system with luminal structure for in vitro mouse spermatogenesis
  - Project is optimizing microfluidic culture conditions
  - CBER provides microfluidic expertise
- Investigating microfluidic human placenta barrier model using human trophoblasts and endothelial cells
  - Prototype under development
  - CBER provides microfluidic expertise



- Verification of novel predictive biomarkers of doxorubicin-induced cardiotoxicity in breast cancer patients
  - Primarily NCTR/CDER/OCE collaboration
  - CBER will provide expertise, if needed, on the confirmation of candidate biomarkers using the Proximity Ligation Assay
- WGS and proteomic approaches to identify genetic markers associated with biofilm formation and host specificity in MRSA
  - CBER peripherally involved due to potential for information to inform vaccine development

Potential future synergistic opportunity

Toxicity and Immune Responses: Respiratory Viruses, Vaccines, Allergens

VITROCELL Cloud – delivers aerosols to air/liquid interface

Harness NCTR's expertise with VITROCELL to expand CBER's capabilities with current use of ALI cultures

- Microparticles (allergens, such as pollens, house dust mites)
- Respiratory viruses
- Mucosal vaccines with and without adjuvants (nano particles, emulsions, agonists of innate immunity)

Air/Liquid interface cell culture for Human Bronchial Epithelial Cells (HBEC)

VITROCELL® technology: allows manipulation of pressure, humidity, droplet size

May improve understanding of impact of test article exposure on lung epithelial cells

Summary

- CBER leverages NCTR expertise to develop methods and approaches to support evaluation of our regulated products.
  - New areas in FY19: lipodomics, metabolomics
- NCTR leverages CBER expertise
  - Expanded FY19 collaborations: microfluidics
- Challenges:
  - Fast pace of scientific innovation:
    - Regulated products and tools used to evaluate
  - Identifying synergistic opportunities that address regulatory and public health priorities
    - Often best accomplished scientist to scientist
  - Funding and timelines
  - Communication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