

# 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



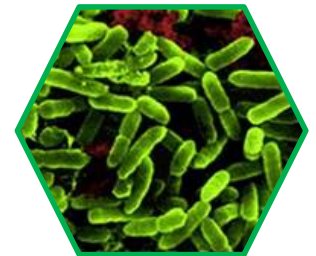
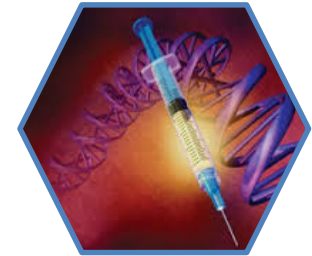
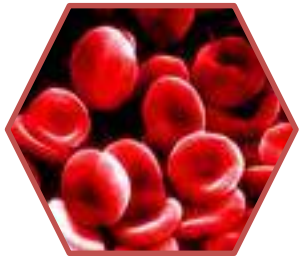


*My comments are an informal communication and represent my own best judgment.*

*These comments do not bind or obligate FDA.*

# Products Regulated by CBER

- Allergens
- 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

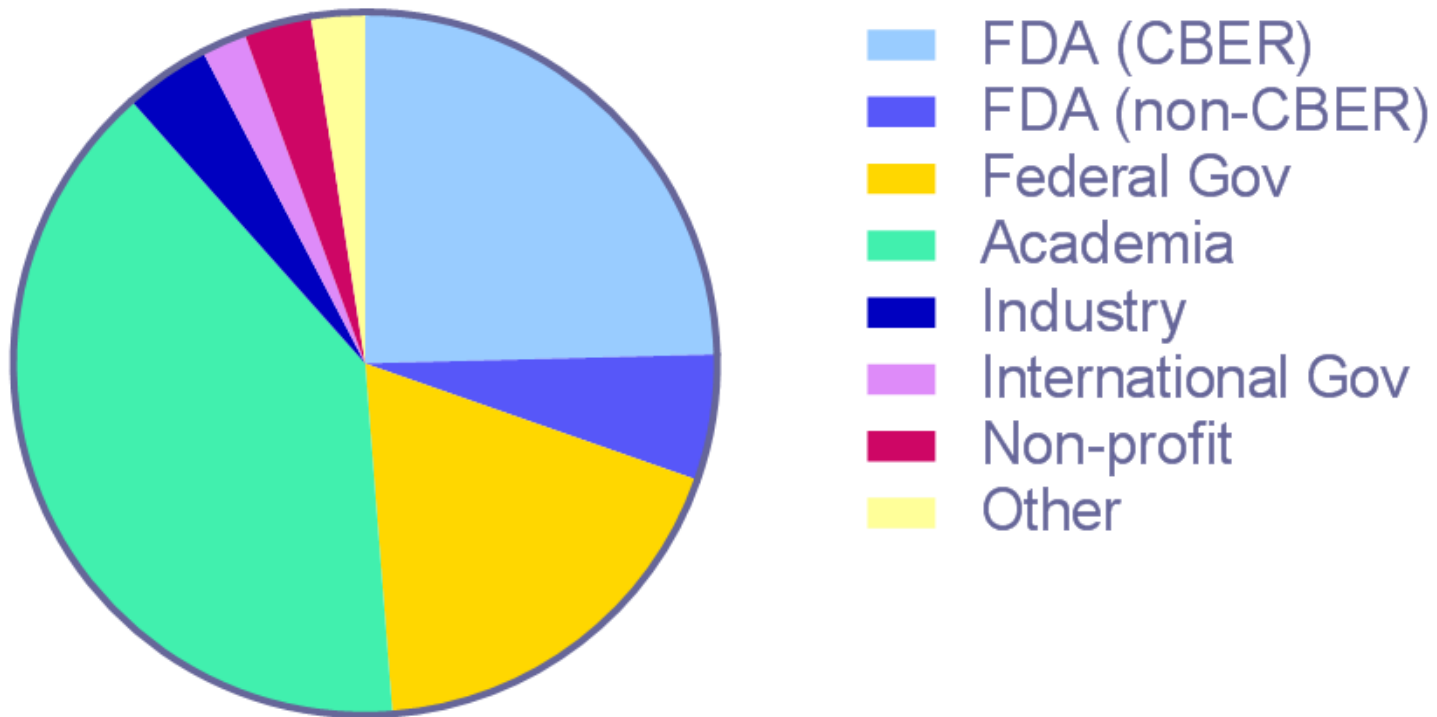
- Core Facilities:
  - Flow cytometry
  - Confocal and electron microscopy
  - Biotechnology
    - ✓ Illumina HiSeq and MiSeq
    - ✓ Oligonucleotide, siRNA, PNA, and peptide synthesis
    - ✓ Peptide and DNA sequencing (ABI, capillary)
    - ✓ Taqman probe synthesis
    - ✓ HPLC; Capillary electrophoresis
    - ✓ 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



Collaborations by Sector

Total=484



# CBER-relevant NCTR Collaborations

- Goal 1: CMC
  - Pathogen detection in fecal microbiota transplantation products: ONGOING, no major updates
  - Detect off-target mutations of gene editing (CBER Goal 2 as well): NEW
  - Identify critical quality attributes on chimeric antigen receptors (CAR-T) (CBER Goal 4 as well):
    - NEW, PENDING Chief Scientist Grant review

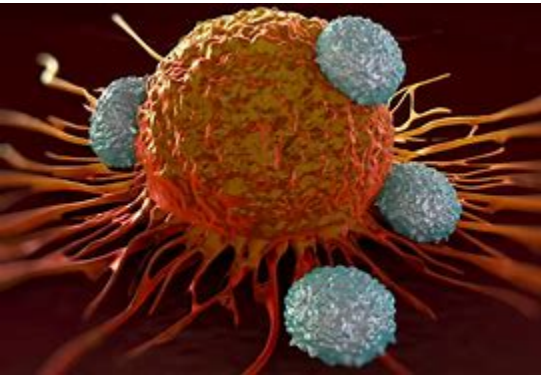




# Detect off-target mutations of gene editing



- *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.



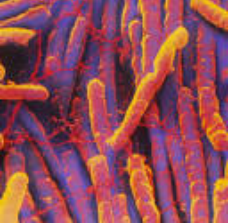
# Identify critical quality attributes on chimeric antigen receptor T cells (CAR-T)



- *Collaborators:* Vijayalakshmi Varma, Sumit Sarkar, Nathan Koonce, Luisa Camacho, Paul Felton (NCTR); Nirjal Bhattarai (CBER)
- *Need:* CBER approved two CAR-T cell products. Many more are in the pipeline. However, it is challenging to identify critical quality attributes (CQAs) of the product that will predict safety and efficacy. Novel in vitro and in vivo models will be used to identify CQAs.
- *Impact:* If successful, the study could provide useful insights to assist with regulatory review of future T-cell-based therapies with regard to product characterization or assessing manufacturing changes on the product.

# CBER-relevant NCTR Collaborations

- Goal 2: Nonclinical
  - Analysis of codon optimized therapeutic proteins using ribosome profiling as a means to evaluate impact of non-synonymous mutations: COMPLETE; Presented at 6 meetings over past two years
  - Bioreactor model to simulate C. difficile-host interactions: ONGOING
  - PK and biodistribution of novel adjuvants (n=2): COMPLETE
    - 2<sup>nd</sup> manuscript drafted, internal CBER clearance
  - Support development of animal model to support norovirus vaccine development: ONGOING



# Bioreactor model to simulate *Clostridium difficile* - host interactions



*Collaborators:* R. Doug Wagner (NCTR); Paul Carlson (CBER)

*Need:* Improved understanding of host-pathogen-microbiota interactions during *C. difficile* infection and fecal microbiota transplantation using a human enterocyte cell line

*Why NCTR:* Research experience in microbiology and microbiome

*Results:*

- Developed hybrid in vitro culture system using human HT-29 enterocyte cells in anaerobic incubation system to show:
  - Cytotoxicity of *C. difficile* and other commensal strains on HT-29
  - Understand immune response when pathogen is alone or added in combination with commensal organisms
  - Metagenomic analysis after coculture
- Mouse challenge model using cefoperazone treatment suggestive that *C. difficile* induced pro-inflammatory cytokines (IL-1-beta, TNF-alpha, IL-2)

*Impact:* Improved understanding may lead to more defined therapeutics in place of FMT



# Support development of animal model to support norovirus vaccine development



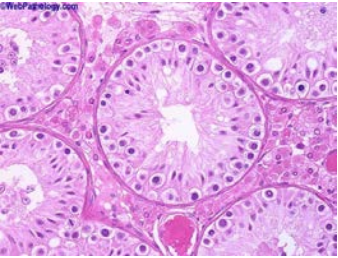
- *Collaborators:* Marli Azevedo (NCTR); Gabriel Parra (CBER)
- *Need:* No animal model for norovirus
- *Why NCTR:* Dr. Azevedo has large number canine samples infected with noroviruses
- *Results:* 10 canine norovirus genomes sequenced (prior to this, no full-length canine norovirus genomes in public DB). Unique characteristics identified that might limit zoonotic potential.
- *Impact:* New insights into zoonotic potential; possibility that some samples may be useful for animal/cell model adaptation

# Other CBER-NCTR Collaborations



- Evaluation of new drugs to treat Chagas disease
  - NCTR developed candidate drugs using SDAR
  - Molecules not synthesized
  - Project on hold
- Exploration of a microfluidic system with luminal structure for in vitro mouse spermatogenesis
  - NEW, protocol submitted, approval pending

# Exploration of a microfluidic system with luminal structure for in vitro mouse spermatogenesis



- *Collaborators:* Noriko Nakamura, William Mattes (NCTR); Kyung Sung (CBER)
- *Need:* Alternative non-animal models for reproductive toxicological studies.
  - NCTR collaborators have developed in vitro testis organ culture with sperm production, but necrosis in the center was observed.
  - CBER collaborator has microfluidic experience that may be able to address oxygen deficiency in current model.
- *Potential Impact:* If successful, model would allow comparison of drug toxicity between mouse, rat, human and intra-species.

# Summary

- CBER leverages NCTR expertise to develop methods and approaches to evaluate our regulated product portfolio.
- Current portfolio of collaborations:
  - New methods to assess cell and gene therapy products
  - Investigating new opportunities for models to assess treatments and vaccines against pathogens with significant morbidity and mortality
- NCTR leverages CBER expertise in some collaborations
- Challenges:
  - Identifying synergistic opportunities – often best accomplished scientist:scientist
  - Lack of funding
  - Difficulty in communication



