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# Overview

**Office of Therapeutic Products (OTP)  
and  
Office of Plasma Protein Therapeutics (OPPT)**

Basil Golding, MD  
Acting Director, OPPT  
Site Visit - Hemostasis Branch

**April 26, 2023**

# Office of Therapeutic Products (OTP)

OFFICE OF THE DIRECTOR  
**Wilson Bryan, MD**  
**Rachael Anatol, PhD**

DIVISION OF  
CELLULAR AND  
GENE THERAPIES  
**Stephen Oh, PhD**  
(acting)

Cell Therapies Branch  
Gene Therapies Branch  
Gene Transfer and  
Immunogenicity Branch  
Cellular and Tissue  
Therapy Branch  
Tumor Vaccine and  
Biotechnology Branch

DIVISION  
PLASMA PROTEIN  
THERAPEUTICS  
Basil Golding, MD  
Mahmood Farshid PhD

EVALUATION AND  
PHARMACOLOGY  
TOXICOLOGY  
Tejashri Purohit-Sheth, MD  
Jaigirdar, Adnan MD

HUMAN TISSUES  
**Scott Brubaker, MD**

REGULATORY  
PROJECT  
MANAGEMENT  
**Ramani Sista, PhD**  
**Lori Tull, BS**

Hemostasis Branch  
Plasma Derivatives  
Branch

General Medicine  
Branch I

General Medicine  
Branch II

Pharmacology-  
Toxicology Branch I

Pharmacology-  
Toxicology Branch II

Oncology Branch  
Clinical Hematology  
Branch

Human Tissue and  
Reproduction Branch

Regulatory Project  
Management Branch I

Regulatory Project  
Management Branch II

Regulatory Project  
Management Branch III

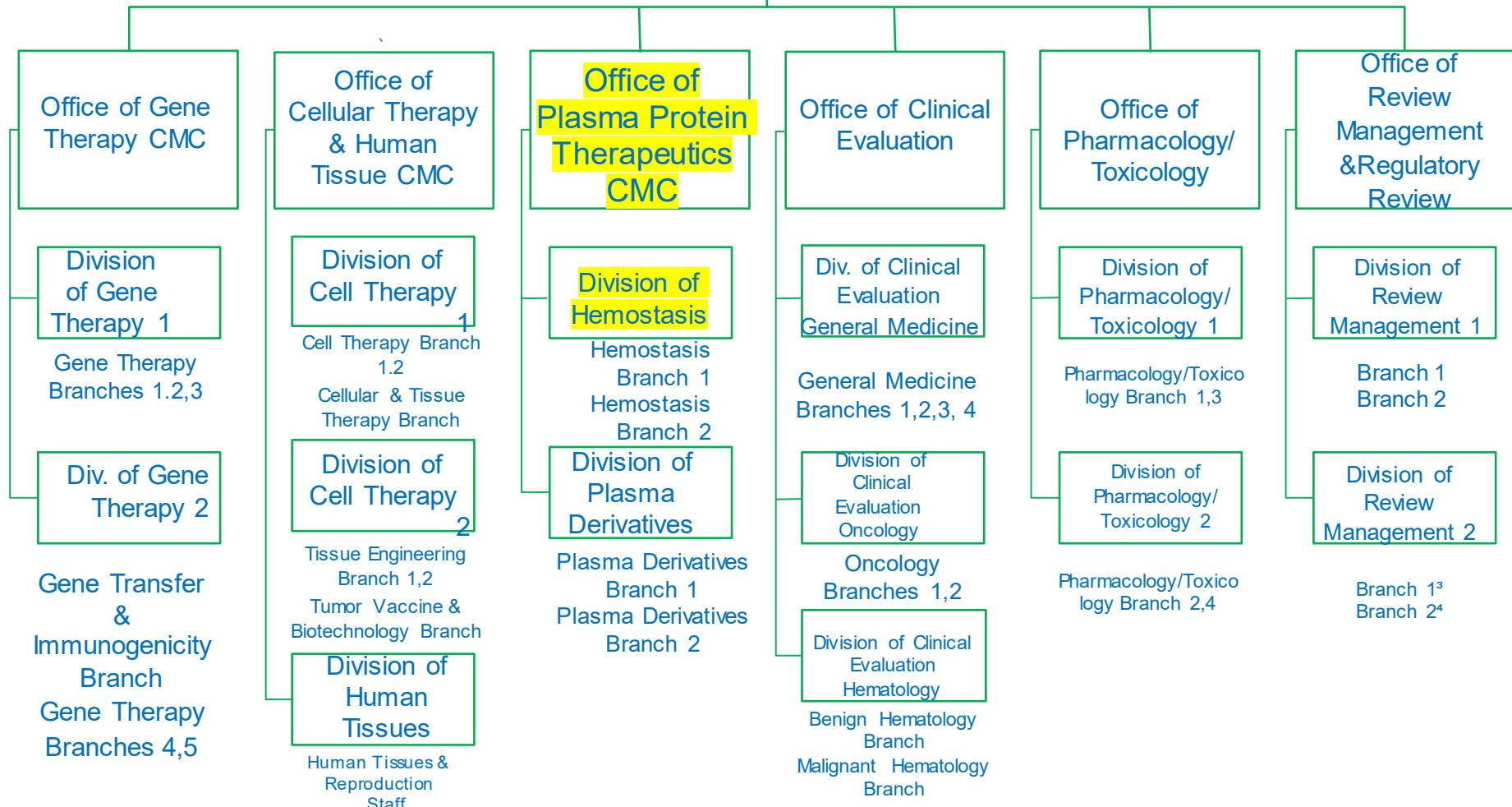
Regulatory Project  
Management Branch IV

 Units that include lab research

# Re-organization: Office of Therapeutic Products (OTP)

## Office of Therapeutic Products

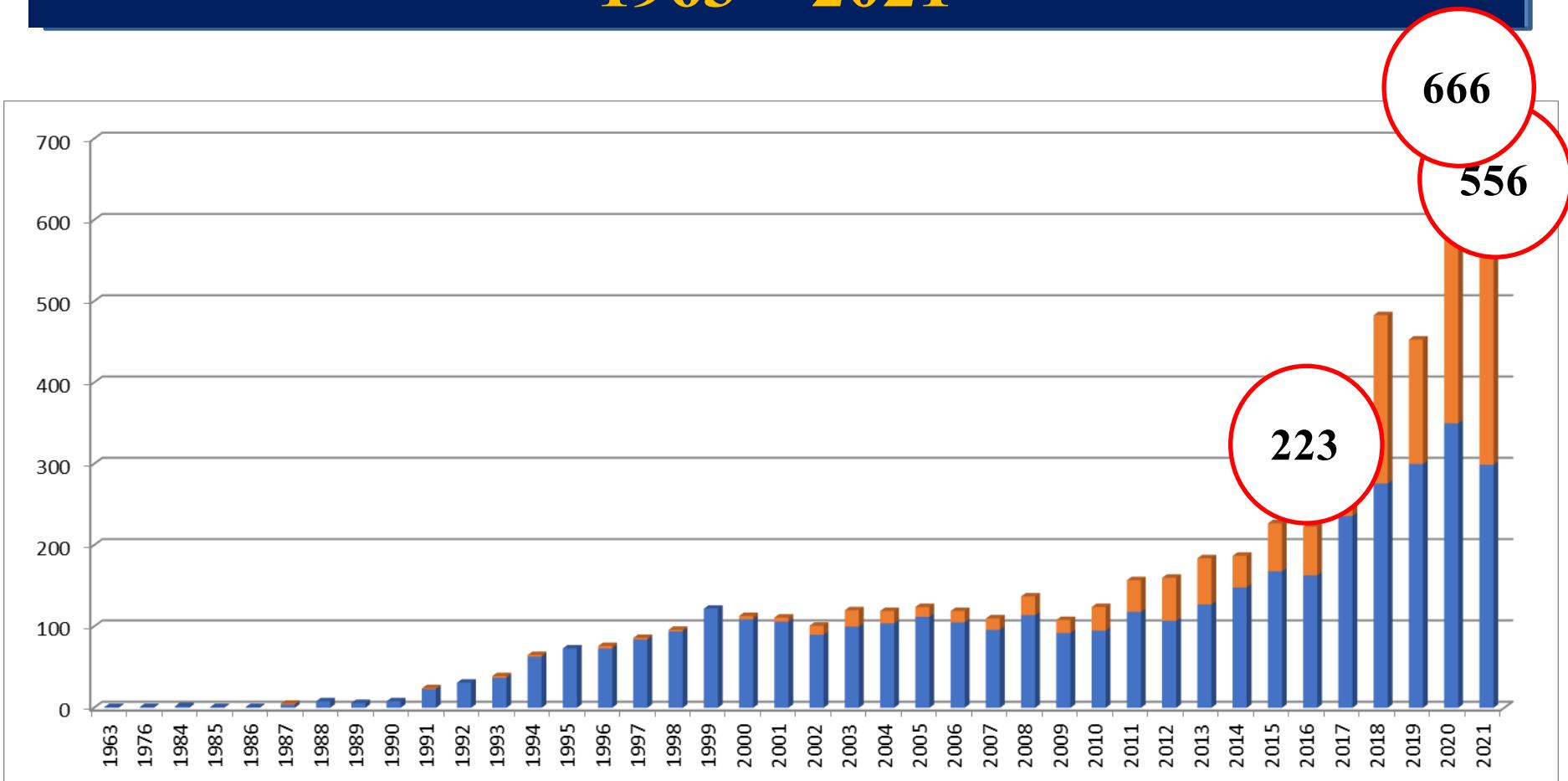
## Administrative Staff Policy & Special Projects Staff



# OTP Products (non-OPPT)

- Stem cell and stem cell-derived products
- Terminally-differentiated cell therapies
- Therapeutic vaccines and other antigen-specific active immunotherapies
- Gene therapies
- Xenotransplantation products
- Tissues and tissue-based products
- Some devices and combination products

# All OTP INDS [i.e., Research and Expanded Access (EA)] 1963 – 2021



# BLA Approvals in 2020 – 2022 (1)

- **SEVENFACT coagulation factor VIIa (recombinant)-jncw**
  - Treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors
- **TECARTUS brexucabtagene autoleucel (CD19)**
  - Relapsed or refractory mantle cell lymphoma
- **BREYANZI lisocabtagene maraleucel (CD19)**
  - Relapsed or refractory large B-cell lymphoma
- **ABECMA idecabtagene vicleucel (BMA)**
  - Relapsed or refractory multiple myeloma

# BLA Approvals in 2021 – 2022

- **STRATAGRAFT**
  - allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat
  - Treatment of adults with thermal burns
- **RYPLAZIM**
  - plasminogen human-tvmh
  - Treatment of plasminogen deficiency type 1 (hypoplasminogenemia)
- **RETHYMIC**
  - allogeneic processed thymus tissue-agdc
  - for immune reconstitution in pediatric patients with congenital athymia

# BLA Approvals in 2021 – 2022 cont.

- **CARVYKTI** - ciltacabtagene autoleucel
  - Is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an antiCD38 monoclonal antibody.
- **ZYNTEGLO** - betibeglogene autotemcel
  - Indicated for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions.
- **SKYSONA** - elivaldogene autotemcel
  - Indicated to slow the progression of neurologic dysfunction in boys 417 years of age with early, active cerebral adrenoleukodystrophy (CALD)
- **Etranacogene-dezaparvovec-drlb**
  - Indicated for Hemophilia B, factor IX deficiency

# OTP Regulatory Science



- 17 laboratories
- 28 publications in 2021-2022
- 36 external conference presentations
- 7 COVID – related research projects

# Office Of Plasma Protein Therapeutics (OPPT)

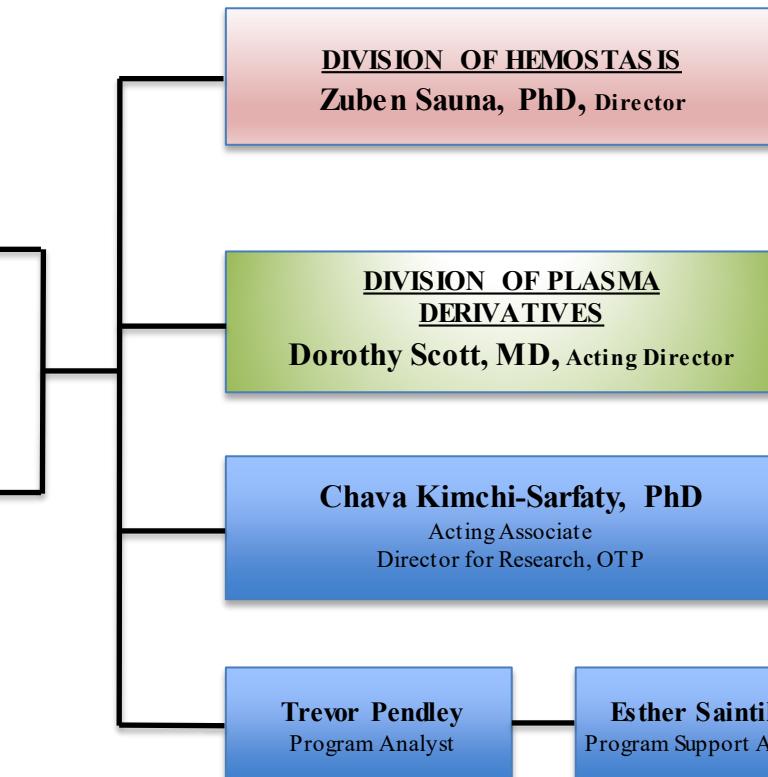
# Office of Plasma Protein Therapeutics - *Organization*



**Basil "Dov" Golding,  
MD**  
Acting Director



**Mahmood Farshid,  
PhD**  
Acting Deputy Director



**Principal Investigators**  
Chava Kimchi-Sarfatty, PhD  
Mikhail Ovanesov, PhD  
Andrey Sarafanov, PhD  
Zuben Sauna, PhD  
17 Staff Scientists and Fellows  
16 ORISE Fellows and Contractors

**Principal Investigators**  
Basil Golding, MD  
Dorothy Scott, MD  
Pei Zhang, MD  
15 Staff Scientists and Fellows  
5 ORISE Fellows and Contractors

# OPPT: Regulatory Function and Other Tasks

- Manufacturing evaluation of products
- Surveillance/adverse effects
- Policy and Guidance documents
- Harmonization: ICH guidance, EMA, Canadian Health Authority
- Liaison meetings
- Communications
- Workshops
- Scientific committees
- Citizen Petitions

# Committees & Working Groups

- Nat'l Institute of Biological Standards and Control (United Kingdom)
- WHO mainly International Standards)
- EDQM (European Pharmacopoeia Expert Group 6B)
- CBER, CDER, and other FDA components
- Multiple USP Committees and Working Groups
- Multiple industry educational groups, e.g. PDA, CASSS, DIA

# OPPT: Regulatory Process

Decisions - based on scientific data showing safety, efficacy and purity

– decision-making process

- internal review
- presentations to Advisory Committees (if needed)
- meetings with manufacturers include:
  - Pre-IND/IDE
  - IND
  - Pre-BLA
  - Mid and Late Cycle Meetings

# OPPT Products – Division of Plasma Derivatives

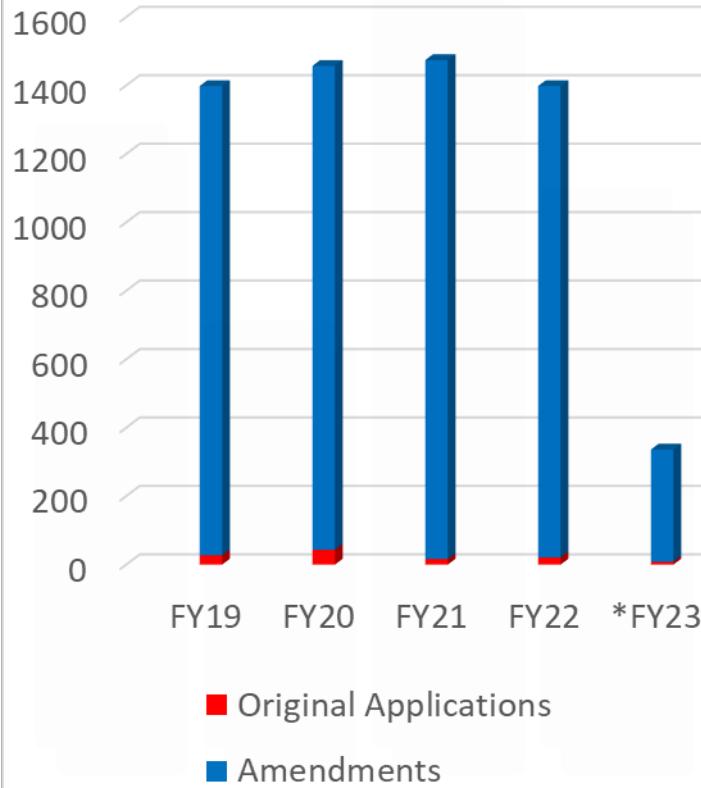
- General Immune globulins
- Specific Immune globulins enriched for particular antibody specificities (infectious agents, toxins)
- Enzyme inhibitors for hereditary deficiencies

# OPPT Products – Division of Hemostasis

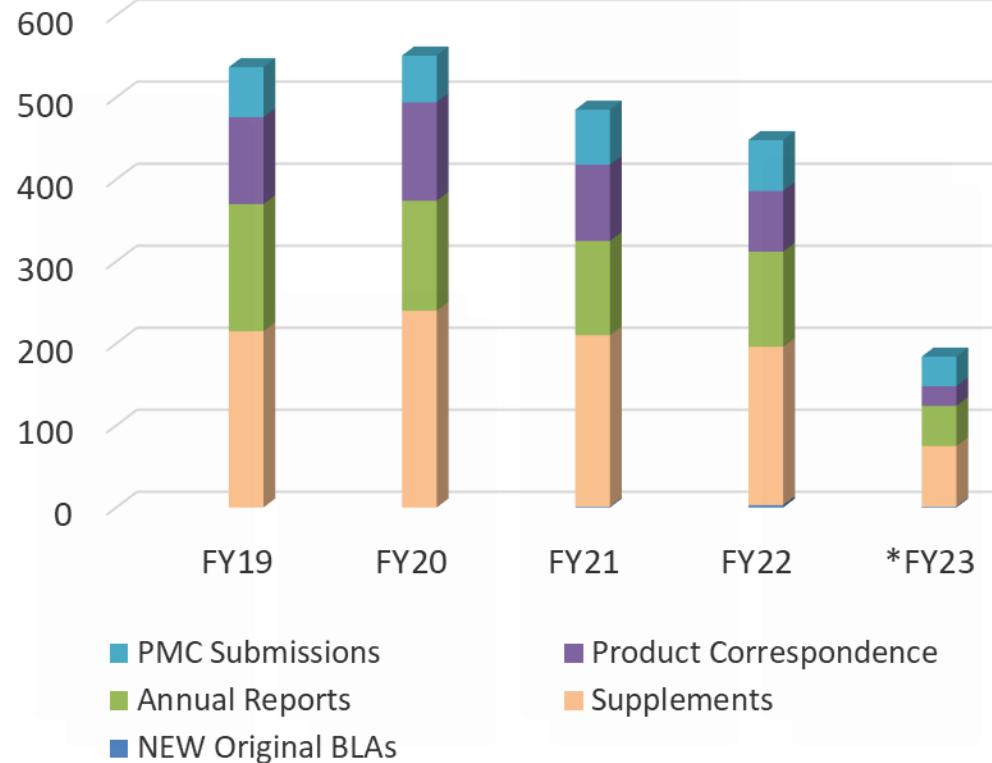
- Coagulation Factors
- Anti-coagulants
- Bypassing Agents
- Hemostatic Agents
- Reversal Agents for Anticoagulants

# OPPT Regulatory Workload Metrics

IND/IDE/MF reviews by OPPT staff



BLA submissions received for review in OPPT



# Scope of OPPT Research

- Study the mechanisms of blood coagulation
- Clearance pathways of Factor VIII and characterization of product-related impurities in recombinant Factor VIII products
- Assay and standard development
- Immunogenicity: Fc-fusion proteins, Factor VIIa, and CRISPR/Cas9
- Pharmacogenomic and codon optimization studies of proteins
- Aggregates in protein products
- Counter-terrorism and Pandemics (e.g. Influenza, COVID-19)
- Efficacy of Immune Globulin Products (Flu, Ebola, Zika, HCV and SARS-CoV-2)

# Publications & Presentations (OPPT)

**26 Publications & 57 Presentations (internal and external) in 2022-2023 (until April 2023)**

## Publication Topics:

- Assays' harmonization
- Therapeutic Protein Immunogenicity
- HLA Donor Optimization
- Synonymous Mutations
- Hemophilia Therapies
- SARS-CoV-2
- Hep B antigens

## Journals:

- Frontiers in Immunology
- J. Thrombosis and Haemostasis
- N Engl J Med
- International Journal of Medical Science
- Scientific Reports

## Presentation Topics:

- Immune Response to CRISPR
- Codon Usage Bias
- Factor VIII Characterization
- International collaboration studies

## Meetings:

- American Society of Hematology
- Int'l Society on Thrombosis and Haemostasis
- Pep Talk
- Drug Industry Association Annual Meeting
- CBER Science symposium

## Looking ahead

OPPT has identified and has plans to address the following gaps in regulatory research:

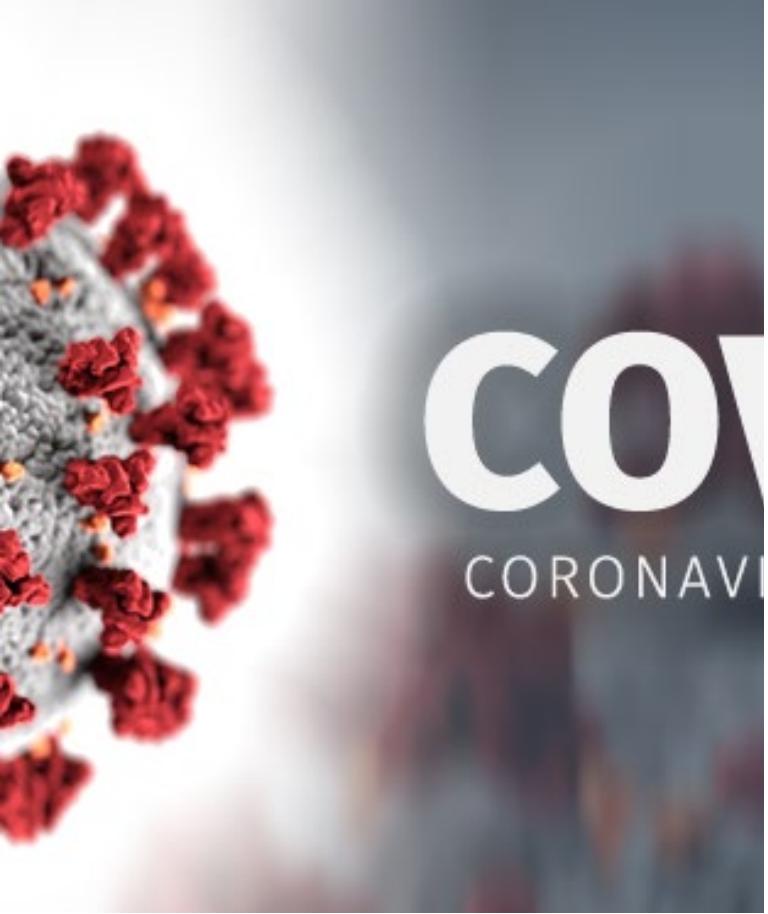
- Bioinformatics approaches to examine immunogenicity and introducing DNA sequence changes for optimizing product yield
- Next generation immune globulins (IGs), such as recombinant polyclonal IGs, modified IGs, and novel IGs against emerging pathogens and toxins
- Safety issues related to platform technologies for protein modifications such as Fc and albumin fusion and pegylated proteins

# Acknowledgements

- Chava Kimchi-Sarfaty
- Robert McElwain
- Trevor Pendley

- Upper Management
- OPPTStaff

Thank You!



# COVID-19

# DPPT research addresses new challenges: COVID-19

- Dosing Considerations for Hyperimmune SARS-CoV-2 IG Based on Hamster Challenge Studies
- Investigating coagulopathies that are associated with mortality following SARS-CoV-2 infection
- Develop methods for rapid screening of convalescent plasma for SARS-CoV-2 neutralizing activity
- Design codon-modified versions of the SARS-CoV-2 virus to attenuate for vaccine use
- Testing of antibodies that neutralize SARS-CoV-2
- Examine binding of coagulation-related proteins to SARS-CoV-2

# Outside Recognition of the Importance of DPPT Research

Projects received FDA or external grants (since 2017):

- BARDA
- OCET Zika Supplemental
- FDA Challenge Grant-Chief Scientist
- FDA Challenge Grant-NanoCores
- FDA Challenge Grant-MCMi
- FDA/NCTR Perinatal Health Center of Excellence
- OCET COVID-19 Supplemental

Projects received CRADA agreements:

- Boston Children's Hospital
- Cleveland State University (based on RO1)

# Anticipated New Products (1)



- **Procoagulants**
  - Factor IX for prevention of surgical and post-partum hemorrhage in patients with severe Factor XI deficiency
  - Recombinant Factor Xa variant for the treatment of patients with intracerebral hemorrhage
  - Human plasma-derived plasminogen for the treatment of ligneous conjunctivitis (topical) and the replacement of plasminogen in plasminogen-deficient patients (intravenous)
  - New fibrin sealant patch and hemostatic agents
  - New fusion proteins of coagulation factors, e.g., with albumin or XTEN or CTP
  - Fibrinogen-Depleted Human Platelet Lysate for treatment of dry eye secondary to Graft vs. Host disease
  - Anti-clotting protease (ADAMTS13)
- **Anticoagulants**
  - Human plasma-derived plasminogen for the treatment of ligneous conjunctivitis (topical) and the replacement of plasminogen in plasminogen-deficient patients (intravenous)

# Anticipated New Products (2)

- **HDL**
  - For the reduction of atherothrombotic events in patients with acute coronary syndrome who are at high-risk of recurrent ischemic events
- **Immune Globulins**
  - COVID-19 immune globulins made from human convalescent plasma
  - Recombinant polyclonal
  - Glycosylation variants
  - Human hyperimmune polyclonal antibodies sourced from transchromosomal animals, e.g. anti-SARS-CoV-2, influenza
  - Oral milk or colostrum-derived bovine Immune Globulin treatments for gastrointestinal diseases
  - New equine-derived antitoxins (*loxoceles*, coral snake, black widow spider)
- **Hemoglobin Scavengers (Haptoglobin, Hemopexin)**
  - Plasma scavenger proteins which bind to cell-free hb heme and transports it to the liver for treatment of adults with stable Sickle Cell Disease

616 Total (IND, IDE, MF and EUA)

61 Master Files

539 INDs

13 IDEs

2 Pending

1 Voided