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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 Tissues and Advanced Therapies (OTAT)

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

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

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

Cell Therapies Branch

Gene Therapies Branch

Gene Transfer and
Immunogenicity Branch

Cellular and Tissue
Therapy Branch

Tumor Vaccine and
Biotechnology Branch

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

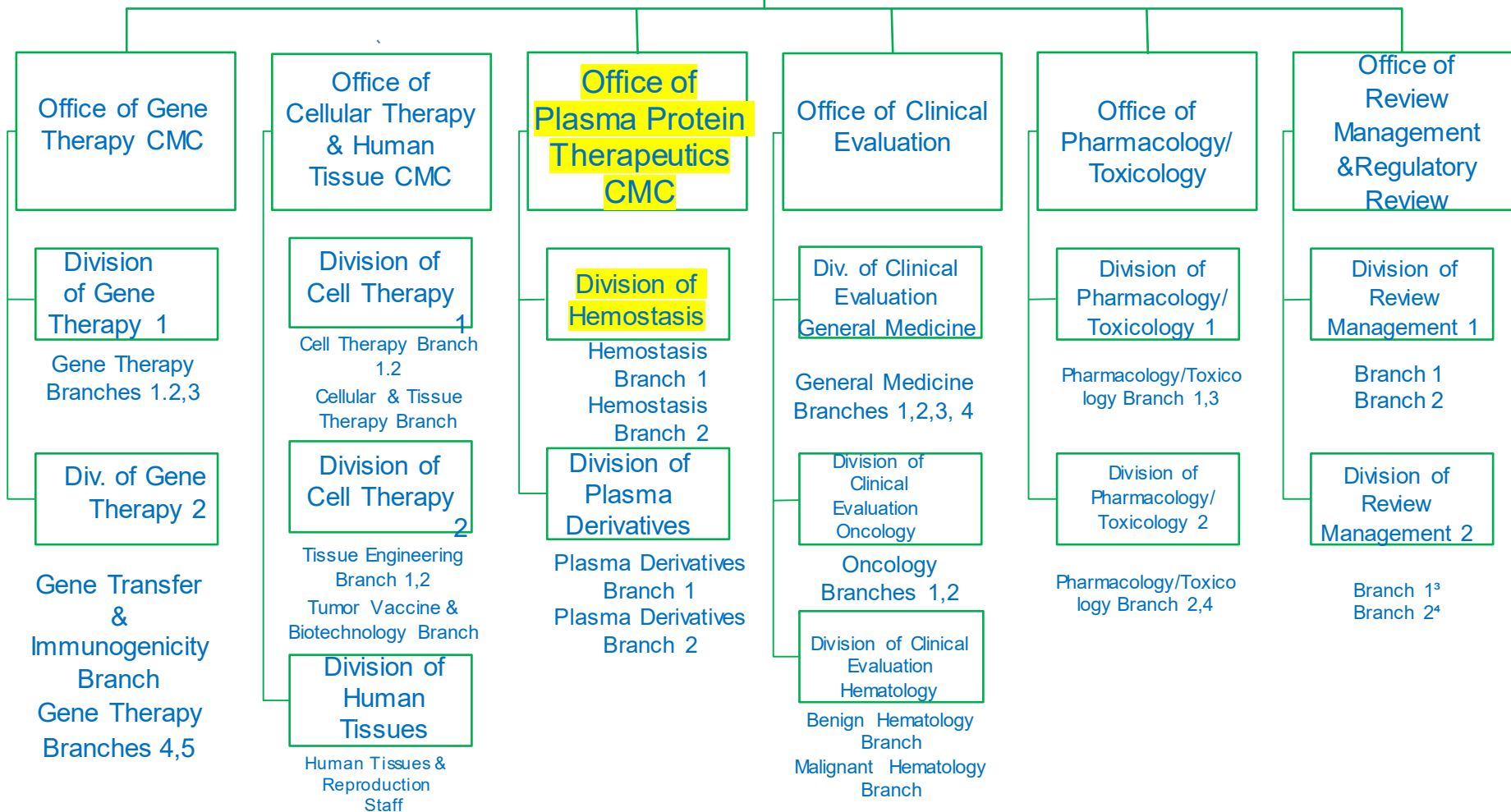
Regulatory Project
Management Branch IV

 Units that include lab research

Re-organization: Office of Therapeutic Products (OTP)

Office of Therapeutic Products

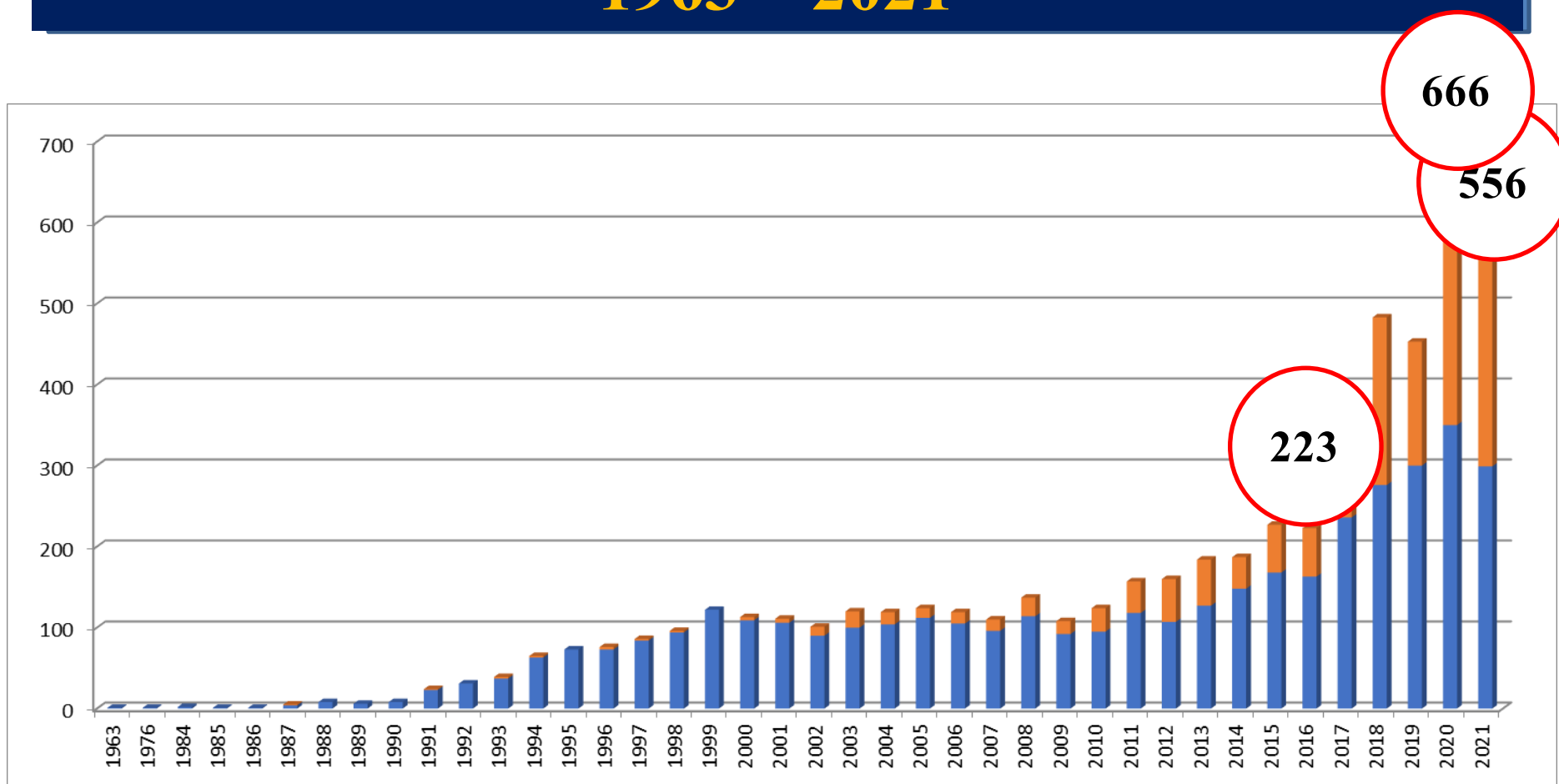
Administrative Staff Policy & Special Projects Staff



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 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD)
- **Etranacogene-dezaparvovec-drlb**
 - Indicated for Hemophilia B, factor IX deficiency

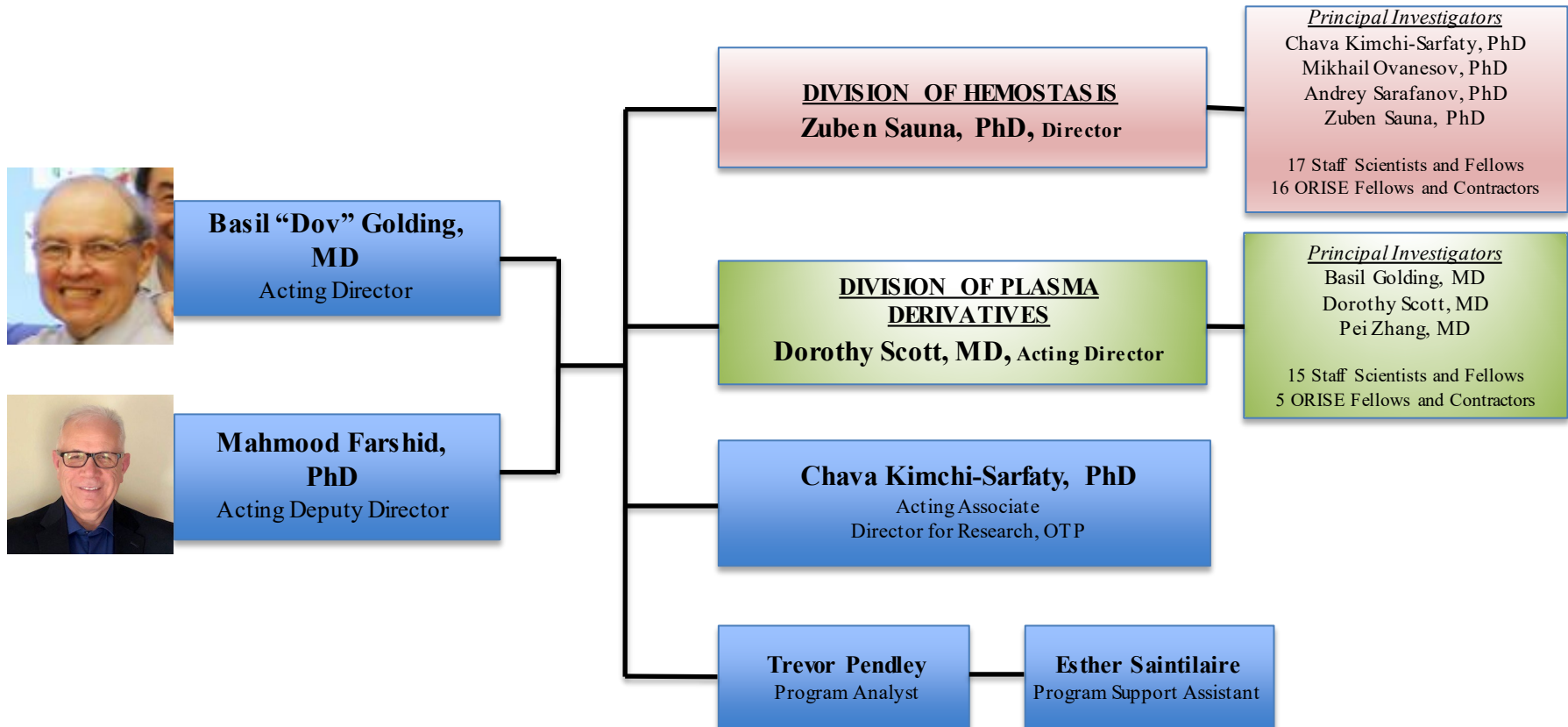
OTP Regulatory Science



- 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*



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

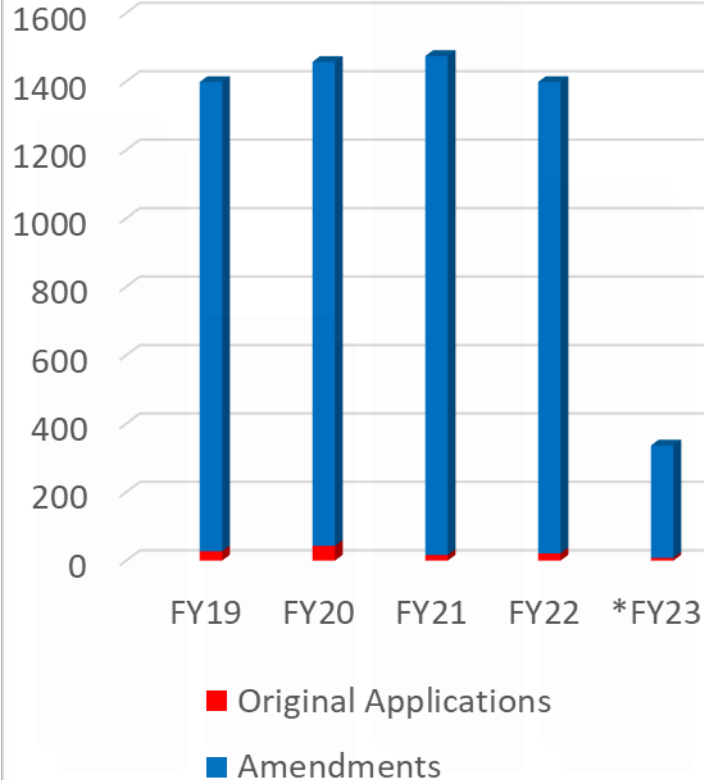
- General Immune globulins
- Specific Immune globulins enriched for particular antibody specificities (infectious agents, toxins)
- Enzyme inhibitors for hereditary deficiencies

OPPT Products – Division of Hemostasis

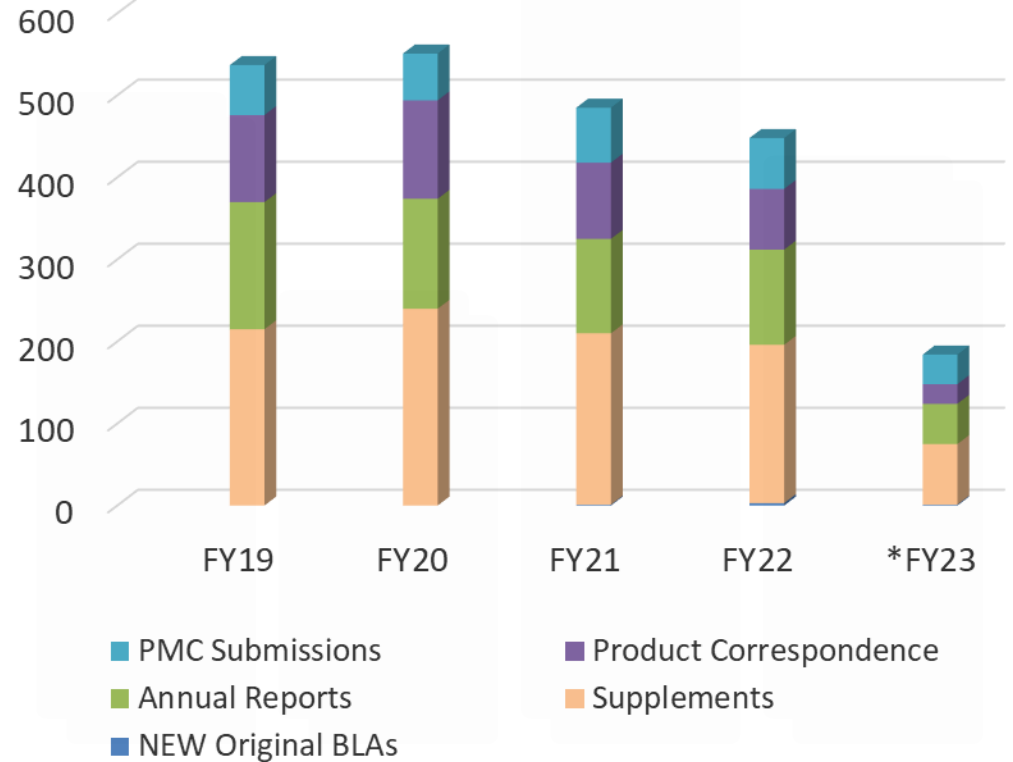
- Coagulation Factors
- Anti-coagulants
- Bypassing Agents
- Hemostatic Agents
- Reversal Agents for Anticoagulants

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:

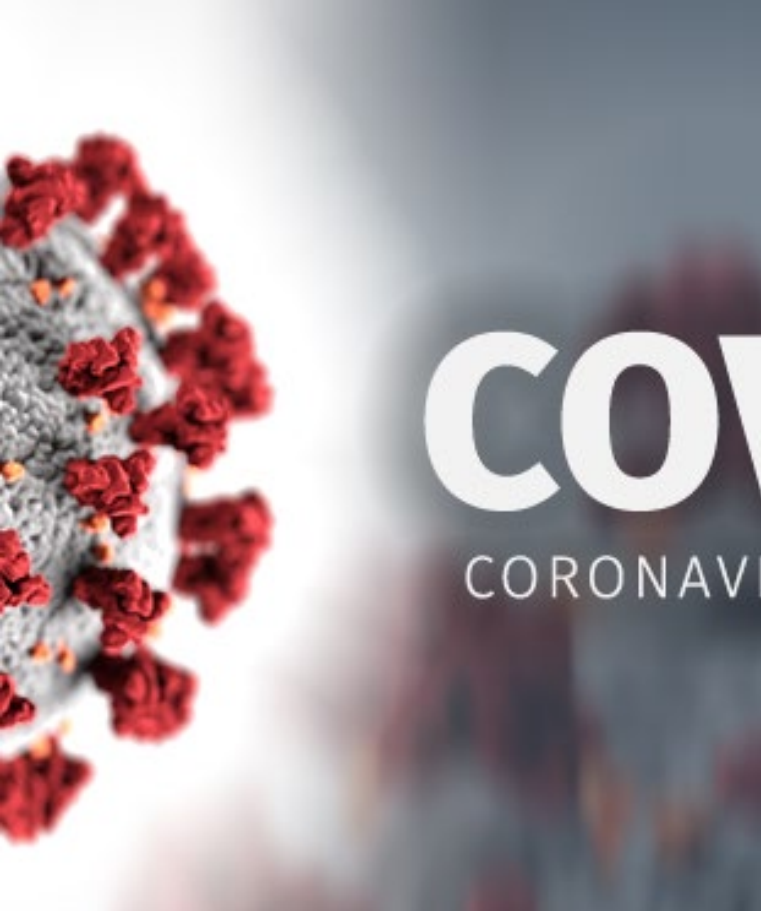
- Bioinformatics approaches to examine immunogenicity and introducing DNA sequence changes for optimizing product yield
- Next generation immune globulins (IGs), such as recombinant polyclonal IGs, modified IGs, and novel IGs against emerging pathogens and toxins
- Safety issues related to platform technologies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