Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

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U.S. FOOD & DRUG ADMINISTRATION

Overview of Research Programs
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies

Cellular, Tissue, and Gene Therapies Advisory Committee Meeting
Review of Intramural Research Program – Gene Transfer and Immunogenicity Branch
March 10, 2022

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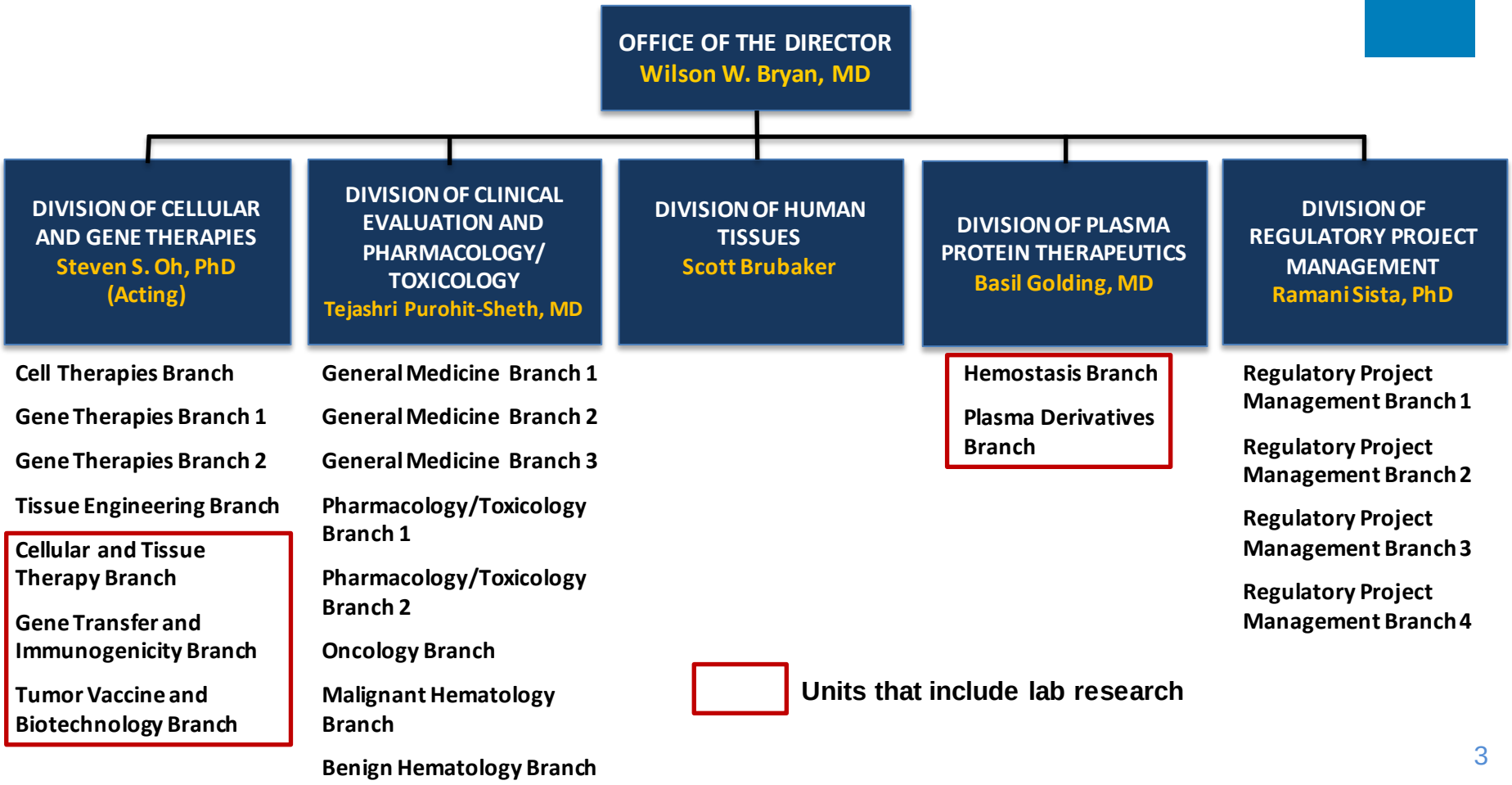
Interim Director, Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies

Outline

- Organizational Structure of Office of Tissues and Advanced Therapies (OTAT)
- OTAT Mission and OTAT Regulated Products
- OTAT Research Goals
- Regulatory Scientist and Researcher Reviewer Model
- Organizational Structure of Division of Cellular and Gene Therapies (DCGT)
- Regulatory Portfolio and DCGT Activities
- DCGT Research and Resources

Office of Tissues and Advanced Therapies (OTAT)



OTAT Mission

The Office of Tissues and Advanced Therapies promotes the public health through collaborative, science-based regulation of medical products. This includes facilitating drug development and ensuring safety of individuals. OTAT's regulatory decisions are data-driven, impartial, and compassionate.

Diversity of OTAT-Regulated Products

Gene therapies

- Ex vivo genetically modified cells
- Non-viral vectors (e.g., plasmids)
- Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
- Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
- Microbial vectors (e.g., Listeria, Salmonella)

Stem cells/stem cell-derived

- Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
- Perinatal (e.g., placental, umbilical cord blood)
- Fetal (e.g., neural)
- Embryonic
- Induced pluripotent stem cells (iPSCs)

Functionally mature/differentiated cells

- e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes

Products for xenotransplantation

Therapeutic vaccines and cellular immunotherapies including antigen-specific active immunotherapies

Blood- and Plasma-derived products

- Coagulation factors
- Fibrin sealants
- Fibrinogen
- Thrombin
- Plasminogen
- Immune globulins
- Anti-toxins
- Venom antisera for snakes, scorpions, and spiders

Combination products

- Engineered tissues/organs

Medical Devices

Tissues

OTAT Research Goals

❑ OTAT Research Goal 1: Chemistry, manufacturing, controls

Enhance quality, consistency, and performance of advanced therapeutics through development of strategies and methods for improved raw materials sourcing, manufacturing as well as product characterization, including test methods, standards, identification of Critical Quality Attributes, and pursuit of related biological investigations.

❑ OTAT Research Goal 2: Preclinical and clinical investigations

Enhance safety and effectiveness of advanced therapeutics through establishment of in silico, in vitro and in vivo preclinical models, and conduct of analyses to increase understanding of clinical trial design issues and patient characteristics that determine outcomes.

❑ OTAT Research Goal 3: Safety issues related to human tissues

Enhance safety and effectiveness of donor screening tests, devices and technologies used in sourcing, manufacturing, processing, and/or testing of tissues and advanced therapeutics.

Researcher Reviewer Model

- Cell and gene therapy products are diverse and rapidly evolving. They use novel approaches to existing regulatory paradigms
- These novel products raise extraordinarily complex issues
- We seek to foster a cadre of Researcher Reviewer scientists who:
  - perform regulatory review and participate in the development of policy and guidance documents to promote product development and patient safety
  - perform research in key areas to support the FDA mission and help sponsors solve product development problems to advance products to the marketplace

Types of Researcher Reviewers

- Principal Investigators (PIs): Permanent and Senior Staff Fellows – researcher-reviewers
- Staff Scientists and Staff Fellows: Researcher-reviewers supporting PI's program; do both review and research
- Technicians: do primarily research, some do limited review work
- Commissioner's Fellows, Inter Agency Oncology Task Force (IOTF), and National Center for Advancing Translational Science (NCATS) Fellows: do research work and trained to do review work
- Postdoctoral Fellows funded as ORISE and other contract mechanisms: do primarily research

Note: Resources are provided to PIs

Responsibilities of PIs

Product review

- INDs, IDEs, PMAs, 510(k)s, HDEs, BLAs, NDAs, master files
- regulatory mentoring

Policy development

- Working groups, policy and guidance development, advisory committees

Outreach

- Pre-submittal advice, scientific and regulatory talks, refereeing and editing for journals, chairing sessions at scientific conferences, scientific collaborations

Research

- Lab management, training/mentoring/supervising, publishing papers, grant writing, leveraging resources, collaboration, serving as expert peer reviewers, scientific peer-review committees, award committees, etc.

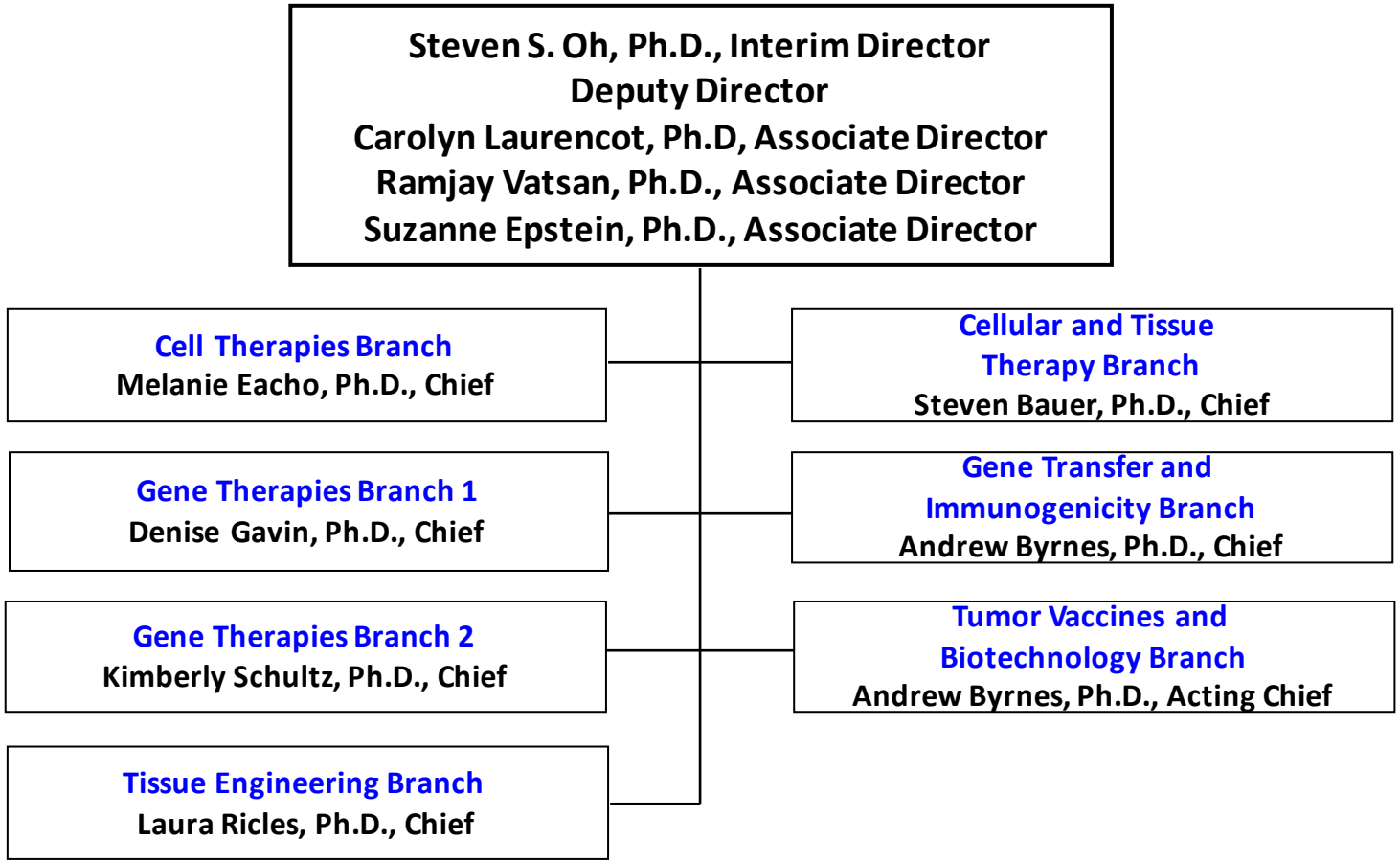
Compliance and enforcement

- Inspections, court testimony, expert witness/declarations

OTAT Regulatory Science

- 21 laboratories
- 51 research publications in 2021
- 47 external conference research presentations
- 7 COVID – related research projects

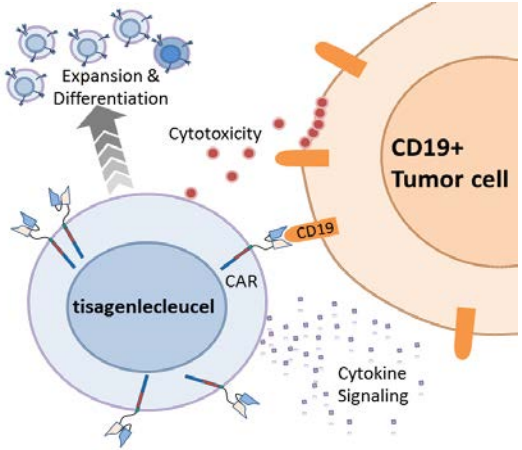
Division of Cellular and Gene Therapies



Approved Gene Therapy Products:
Advanced Therapies at the Leading Edge

FDA News Release (August 30, 2017): FDA approval brings first gene therapy to the United States

- CAR T-cell therapy [Kymriah (tisagenlecleucel)] approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia



FDA News Release (October 18, 2017):

- Yescarta (axicabtagene ciloleucel) is the second gene therapy product approved in the U.S. Indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (DLBCL)

Approved Gene Therapy Products

- KYMRIAH (tisagenlecleucel)
- YESCARTA (axicabtagene ciloleucel)
- TECARTUS (brexucabtagene autoleucel)
- BREYANZI (lisocabtagene maraleucel)
- ABECMA (idecabtagene vicleucel)
- LUXTURNA (voretigene neparvovec-rzyl)
- ZOLGENSMA (onasemnogene abeparvovec-xioi)
- CARVYKTI (ciltacabtagene autoleucel)

Approved Cellular Therapy Products

- PROVENGE (sipuleucel-T)
- Hematopoietic Progenitor Cells, Cord Blood
- LAVIV (azficel-T)
- GINTUIT (allogeneic Cultured Keratinocytes and Fibroblasts in bovine collagen)
- MACI (autologous Cultured Chondrocytes on porcine collagen membrane)
- STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat)
- RETHYMIC (allogeneic processed thymus tissue-agdc)

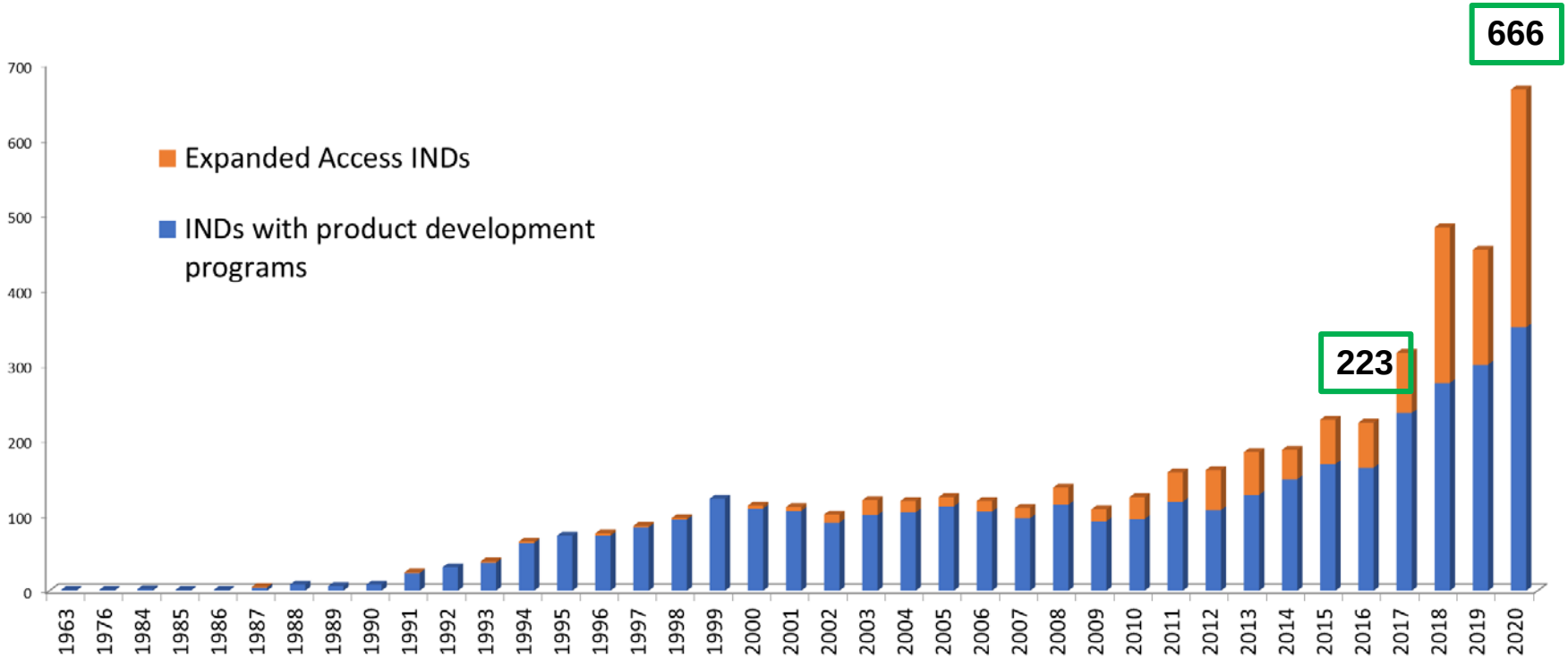
DCGT Activities

- Review, evaluate and take appropriate action on product applications submitted by manufacturers of cell therapy, gene therapy, and tissue-engineering products
  - IND, BLA, IDE, PMA, HDE, 510(k) –original submissions, amendments, and supplements
- CATT, INTERACT (pre-pre-IND), pre-IND, and pre-IDE submission advice
- Participate in inspections of manufacturing facilities for compliance with applicable standards, and other compliance activities including court cases
- Develop policy and procedures governing the pre-market review and evaluation of cellular and gene therapy products in keeping with the provisions of the PHS Act and applicable provisions of the FD&C Act

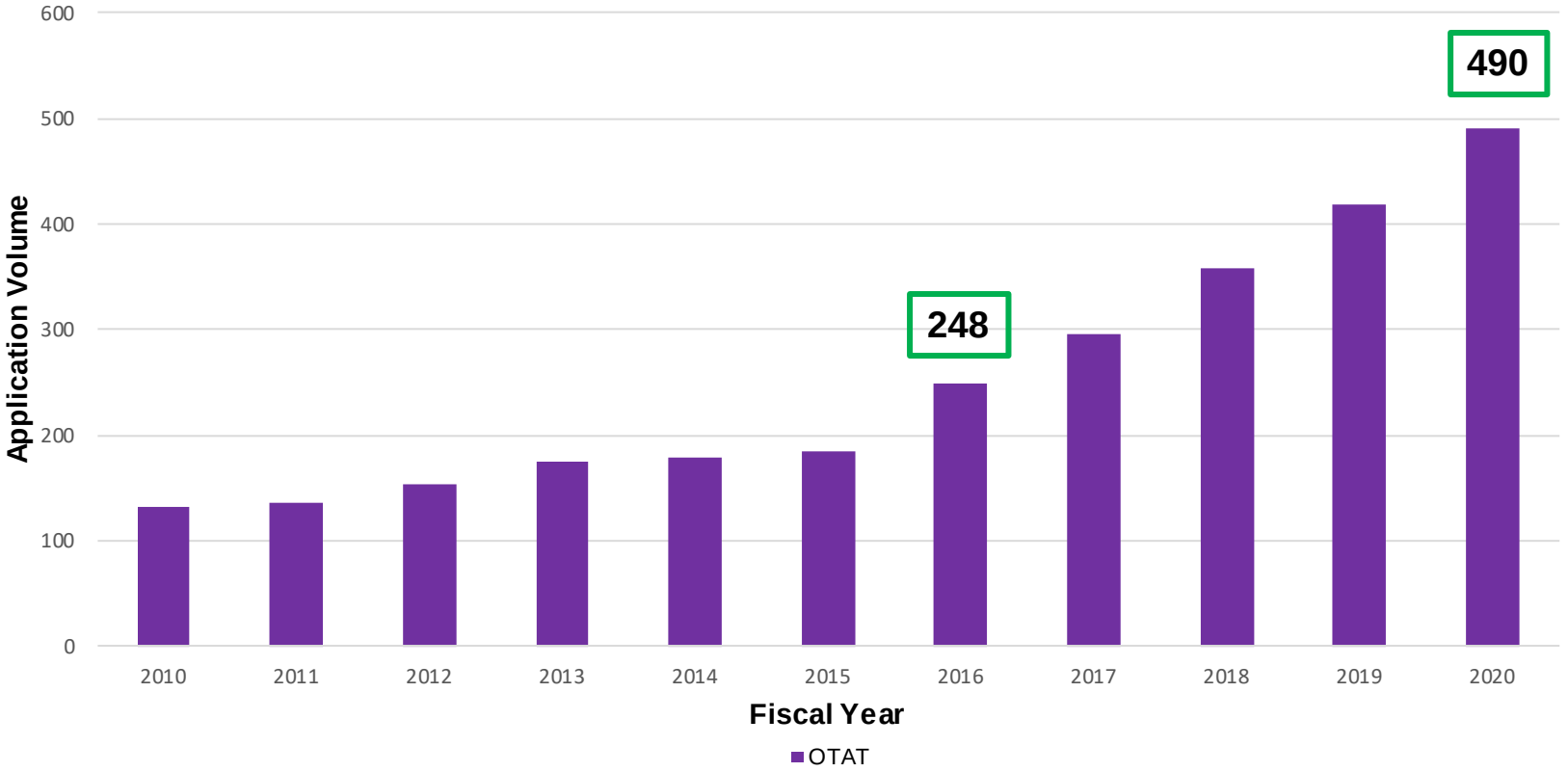
DCGT Activities contd..

- Development of FDA Guidances for the regulation of tissues, cellular, and gene therapy and tissue engineering products –
  - 11+ Guidances in last 2 years
- Perform research to support review and progress towards safe and effective medical products
- Consultation, Grant Review and Education
  - Provide scientific and technical advice to other CBER Offices, FDA Centers, Government Agencies, sponsors
  - Advisory committee meetings
- Community Outreach (professional societies, patient advocacy)
- Partnerships (Standards Development Organizations, Public Private Partnership, NIH, NIST, Global regulatory authorities)
- Counterterrorism activities (Continuity of Operations etc.)

All OTAT INDs submitted (1963 – 2020)



All OTAT Meetings (Type A, B, C, & other)



Breakthrough Therapy (BTD) and Regenerative Medicine Advanced Therapy (RMAT) Designations

- OTAT has received several hundred BTD and RMAT requests, each of which needs careful evaluation.
- When BTD or RMAT has been granted, DCGT reviewers provide intensive guidance on CMC to facilitate efficient drug development
- Such guidance could begin as early as Phase 1, illustrating an intense level of time commitment by reviewers and leadership

Current DCGT Research Areas

- **Virology**
  - Retroviruses, lentivirus, adenovirus, AAV
- **Immunology**
  - Immune responses to viral vectors, transgene products
- **Stem Cell and developmental biology**
  - Control of differentiation in animal models
  - Cell fate and survival, stem cell biology
- **Cancer biology/Immunology**
  - Molecular biomarkers, cancer vaccines, immunotherapy, animal models
- **Biotechnology**
  - Genome editing, Advanced Manufacturing, genomics, flow cytometry, proteomics, transgenics, tissue engineering
- **Multipotent Stromal Cells (MSC) Consortium:** MSC attributes as related to safety and efficacy
- **Tissue safety, function and availability:** Pyrosequencing and WGS

DCGT Resources: Budget

- **Budget Authority** – Productivity is assessed annually
- Some PIs supplement research funding from **internal and/or external grants** e.g.,
  - Chief Scientist Challenge Grants
  - 21st Century Cures, Advanced Manufacturing and COVID funds
  - Modernizing Science, Critical Path (CP), Medical Counter Measure (MCM), and Pan flu
  - Office of Science and Health Coordination (OSHC)
  - Department of Defense (DOD)
  - Biomedical Advanced Research Development Authority (BARDA)
  - Cooperative Research Development Agreement (CRADAs)
  - Royalties from patents

Summary

Roles of Research in OTAT:

- ❑ Provide in-house, hands-on expertise in cutting-edge areas
- ❑ Facilitate product development by addressing challenges encountered and helping develop approaches, guidance
- ❑ Increase public confidence in and acceptance of novel technologies by addressing concerns

Acknowledgements

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