U.S. FOOD & DRUG ADMINISTRATION

Regenerative Medicine and Neurodegenerative Disorders: Regulatory Considerations

CIRM
Brainstorming Neurodegeneration

April 15, 2019

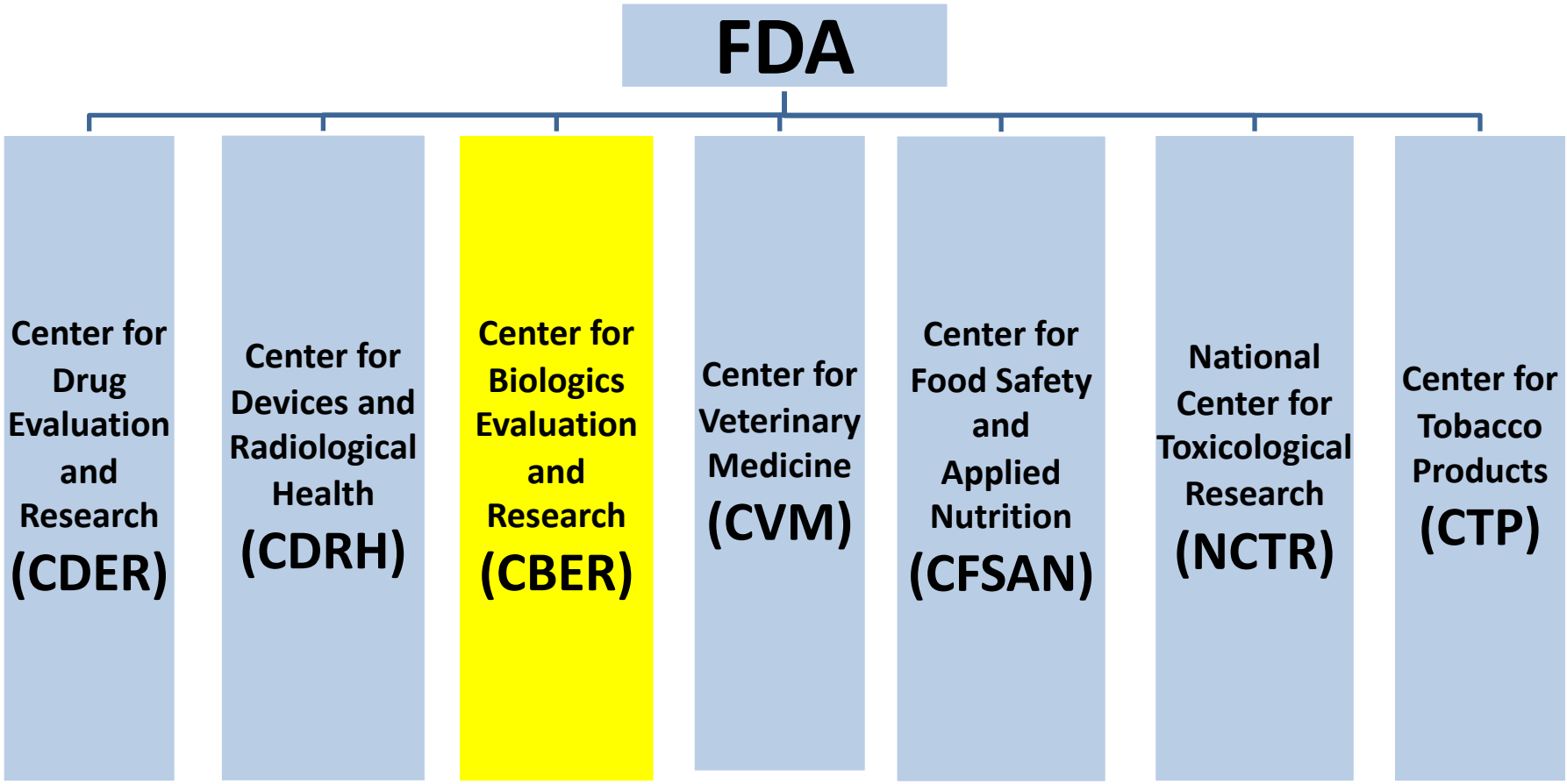
Wilson W. Bryan, MD

FDA Mission

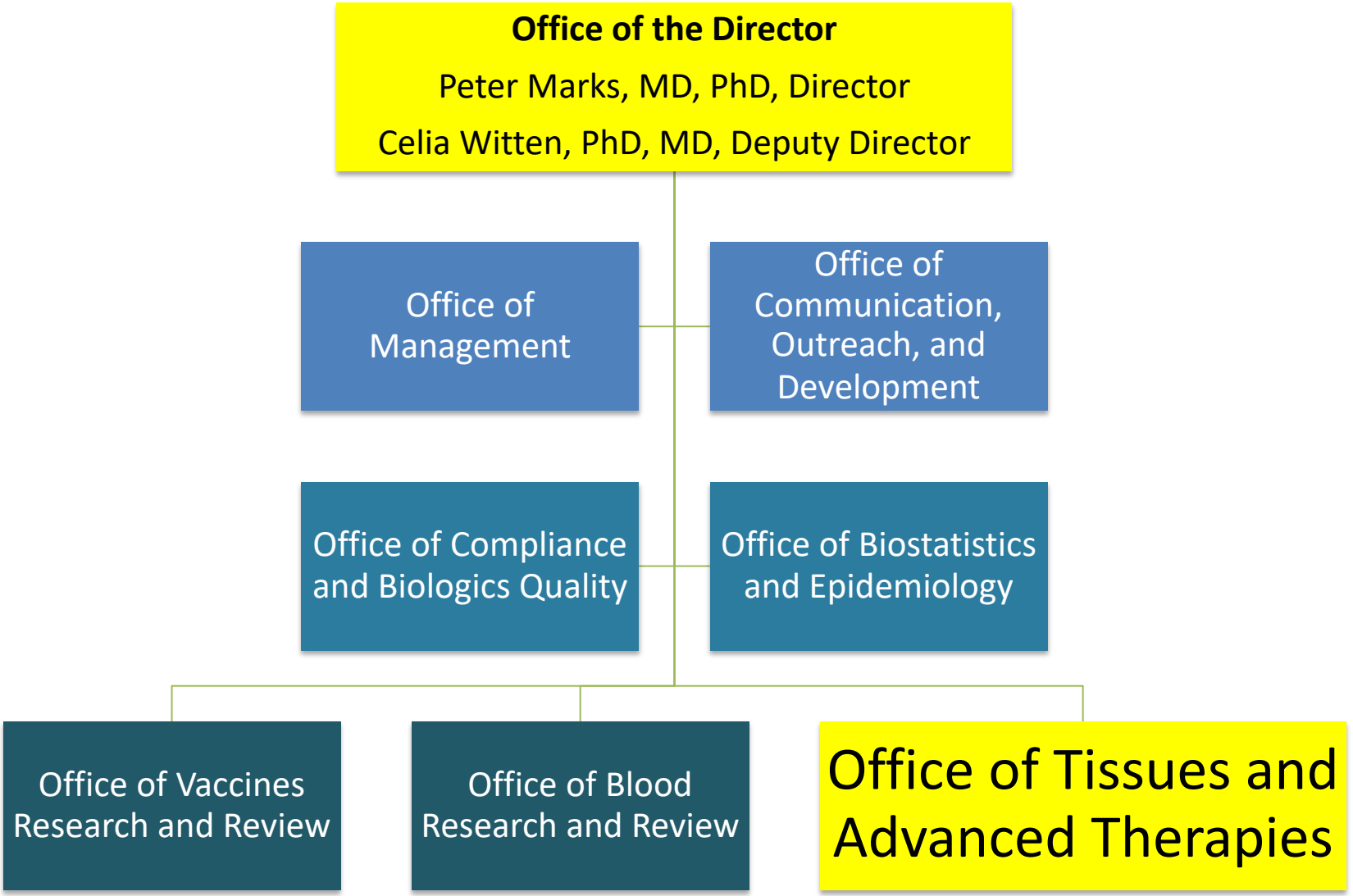
- … protecting the public health by **ensuring the safety**, efficacy, and security of human and veterinary drugs, biological products, and medical devices; …

- … advancing the public health by helping to **speed innovations** that make medical products more effective, safer, and more affordable …

FDA Organization



Center for Biologics Evaluation and Research (CBER)



Diversity of OTAT-Regulated Products

- **Gene therapies (GT)**
  - 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)
- **Products for xenotransplantation**
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **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
  - Snake venom antisera
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Tissues**

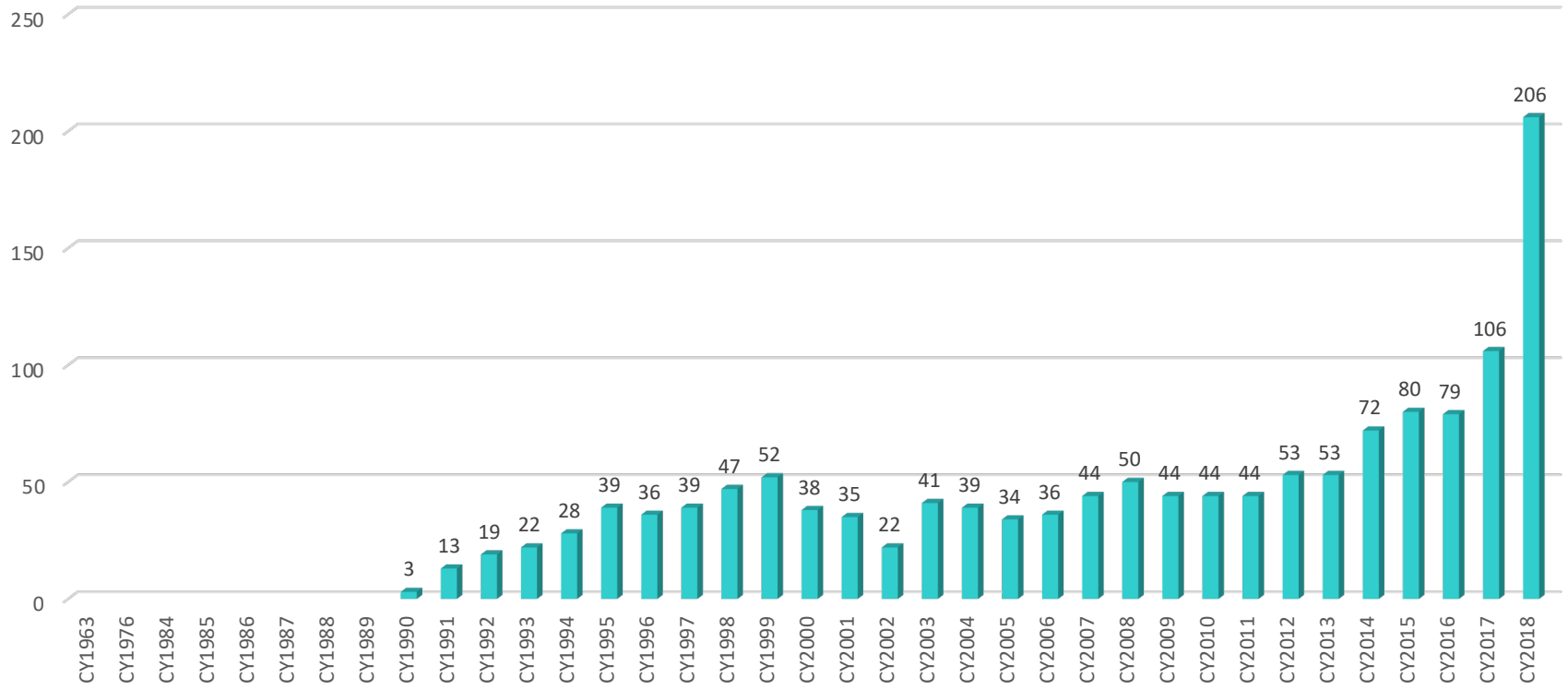
Applications to FDA

- Clinical Development (Clinical Trials)
  - **IND: Investigational New Drug Application**
    - **For drugs and biologics**
  - IDE: Investigational Device Exemption Application

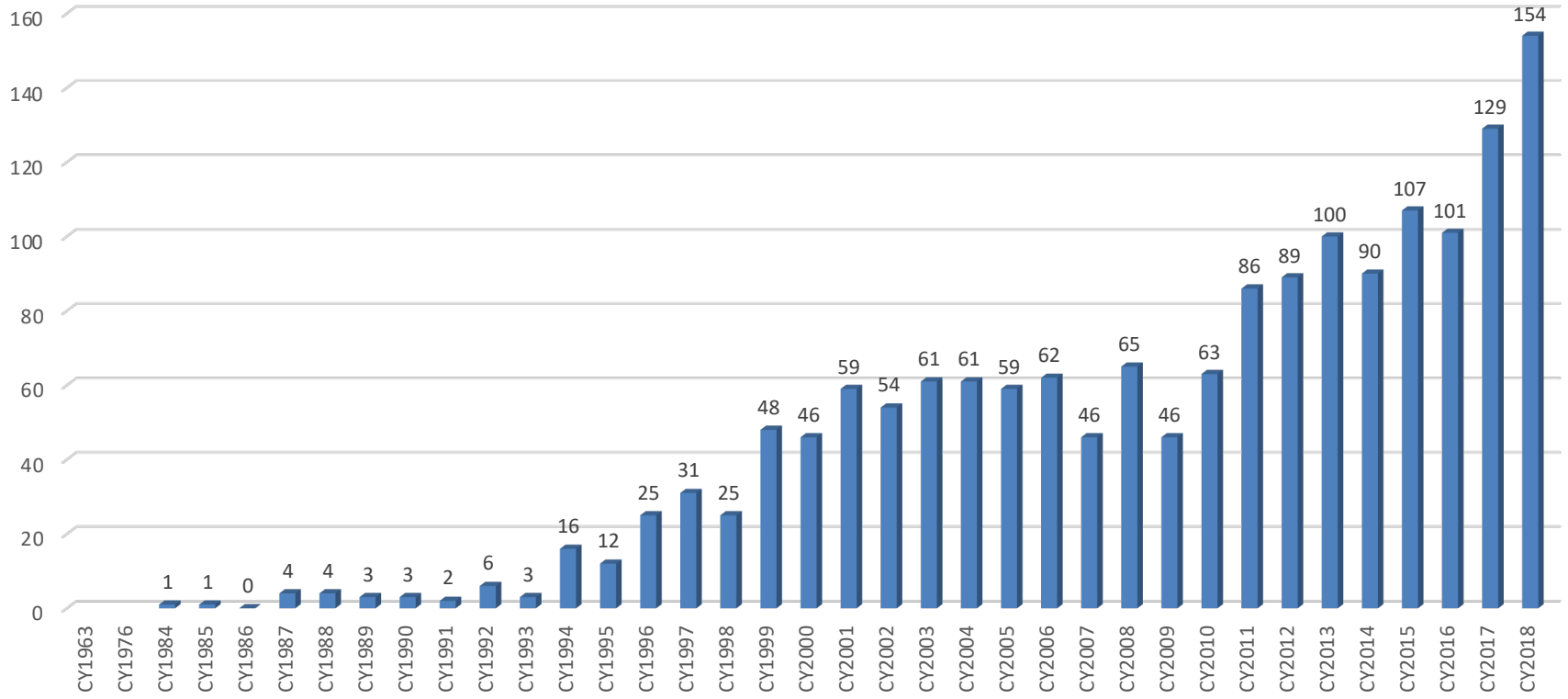
- Marketing
  - BLA: Biologics License Application
  - NDA: New Drug Application
  - Devices:

    Premarket Approval (PMA) or 510k Application

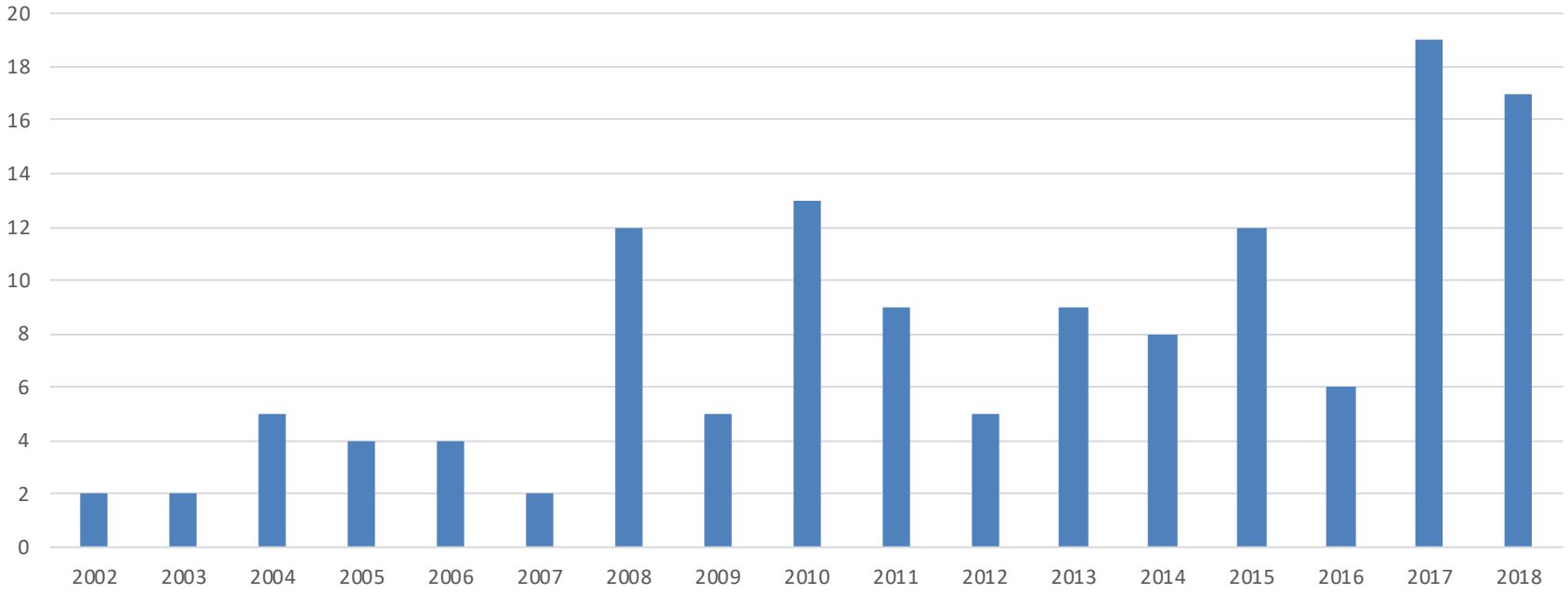
IND Submissions with Gene Therapy Products, CY 1963 – 2018



IND Submissions with Cell Therapy Products, CY 1963 – 2018



IND Submissions for Neurology Indications, 2002-2018



Expedited Programs for Drugs or Biologics

- During development (IND): Designations
  - Fast Track
  - Breakthrough
  - Regenerative Medicine Advanced Therapy
- Marketing Application (NDA or BLA)
  - Priority Review
  - Accelerated Approval

21st Century Cures Act
December 13, 2016

21st Century Cures Act
Section 3033: Definition of Regenerative Medicine Therapy (RMT)

Includes cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act …

Definition of Regenerative Medicine Therapy (RMT)

- Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions
- Interprets RMT definition to also include:
  - Gene therapies that lead to a sustained effect on cells or tissues
  - Certain xenogeneic cell therapies

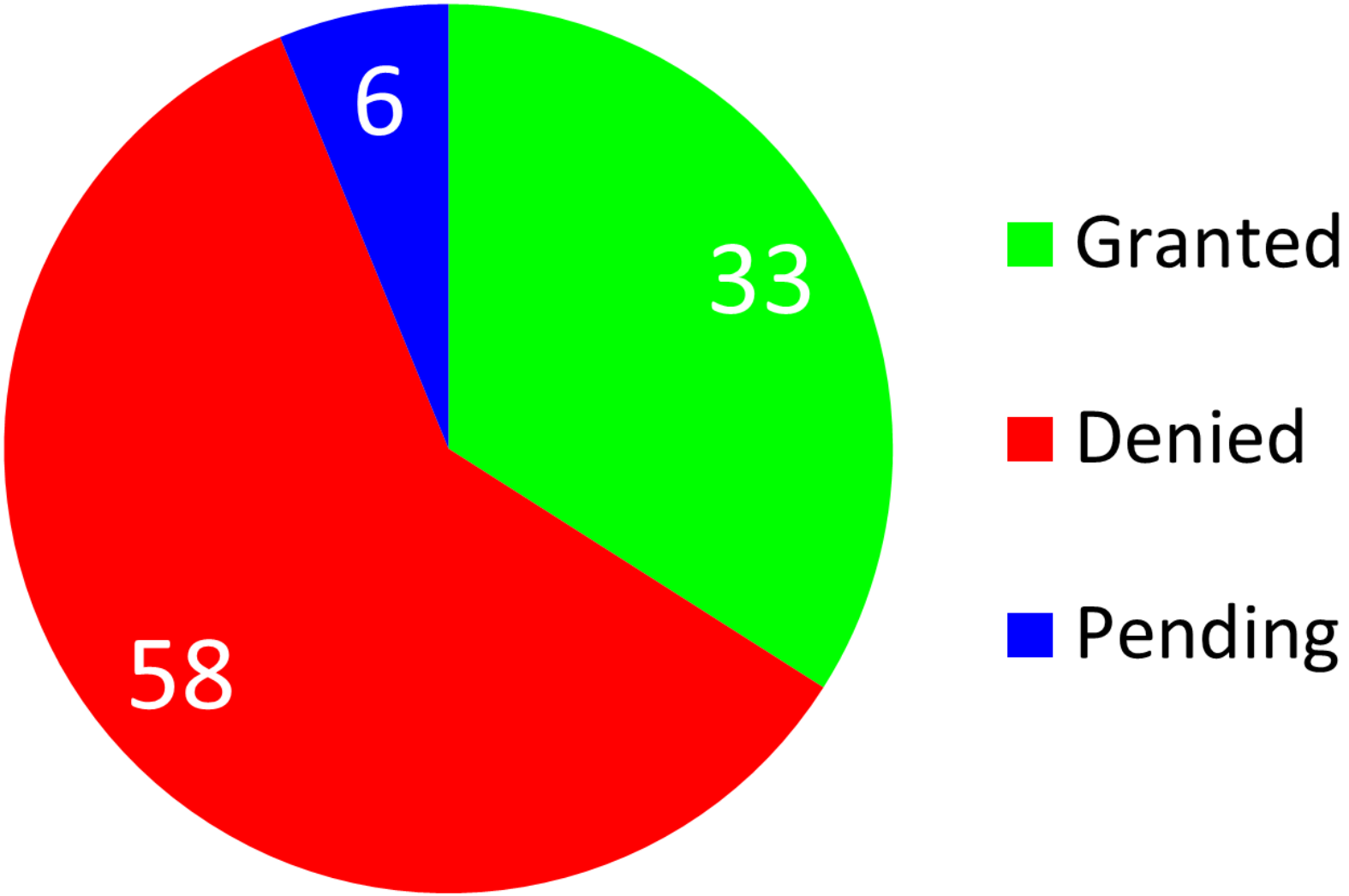
Section 3033: Regenerative Medicine Advanced Therapy (RMAT) Designation

- Creates program for designation of regenerative medicine advanced therapies
- A drug is eligible for designation if:
  - It is a regenerative medicine therapy
  - The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
  - Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition

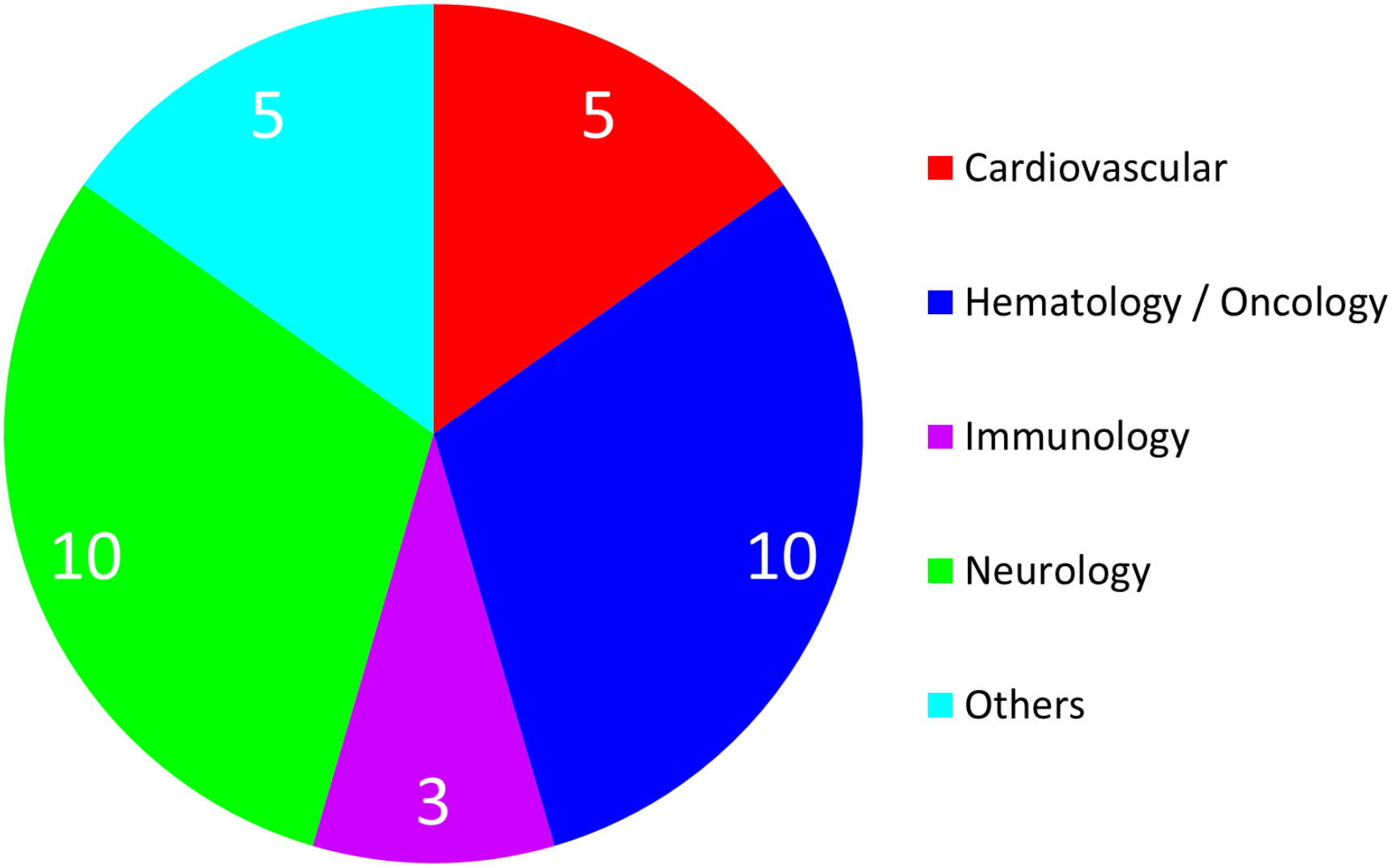
Benefits of RMAT Designation

- Interactions with FDA to expedite development and review of regenerative medicine advanced therapies
  - Benefits available to breakthrough therapies
  - Including early discussions of any potential surrogate or intermediate endpoints to support accelerated approval

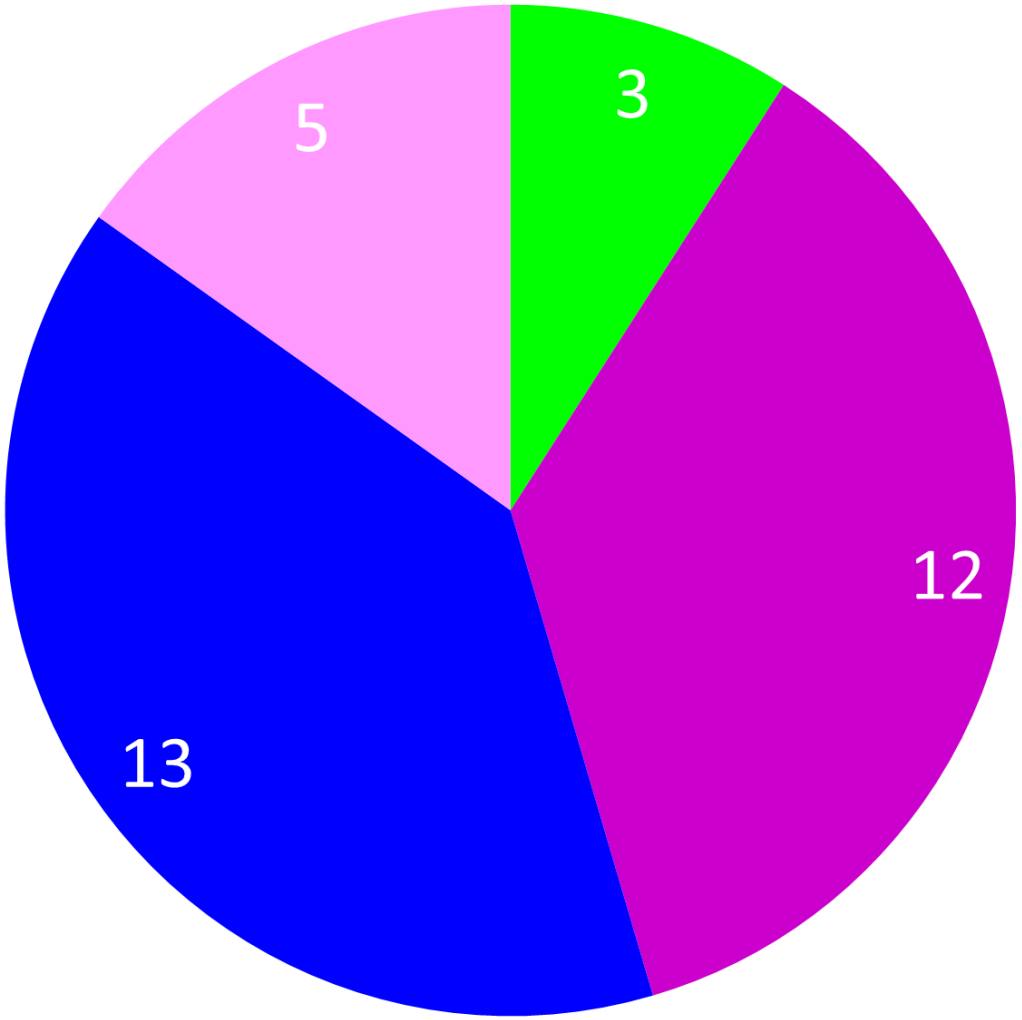
RMAT Designation Requests Status - as of April 13, 2019



Granted RMAT Designation Requests Specialties
- as of April 13, 2019



Granted RMAT Designation Requests
- Distribution by Product Type

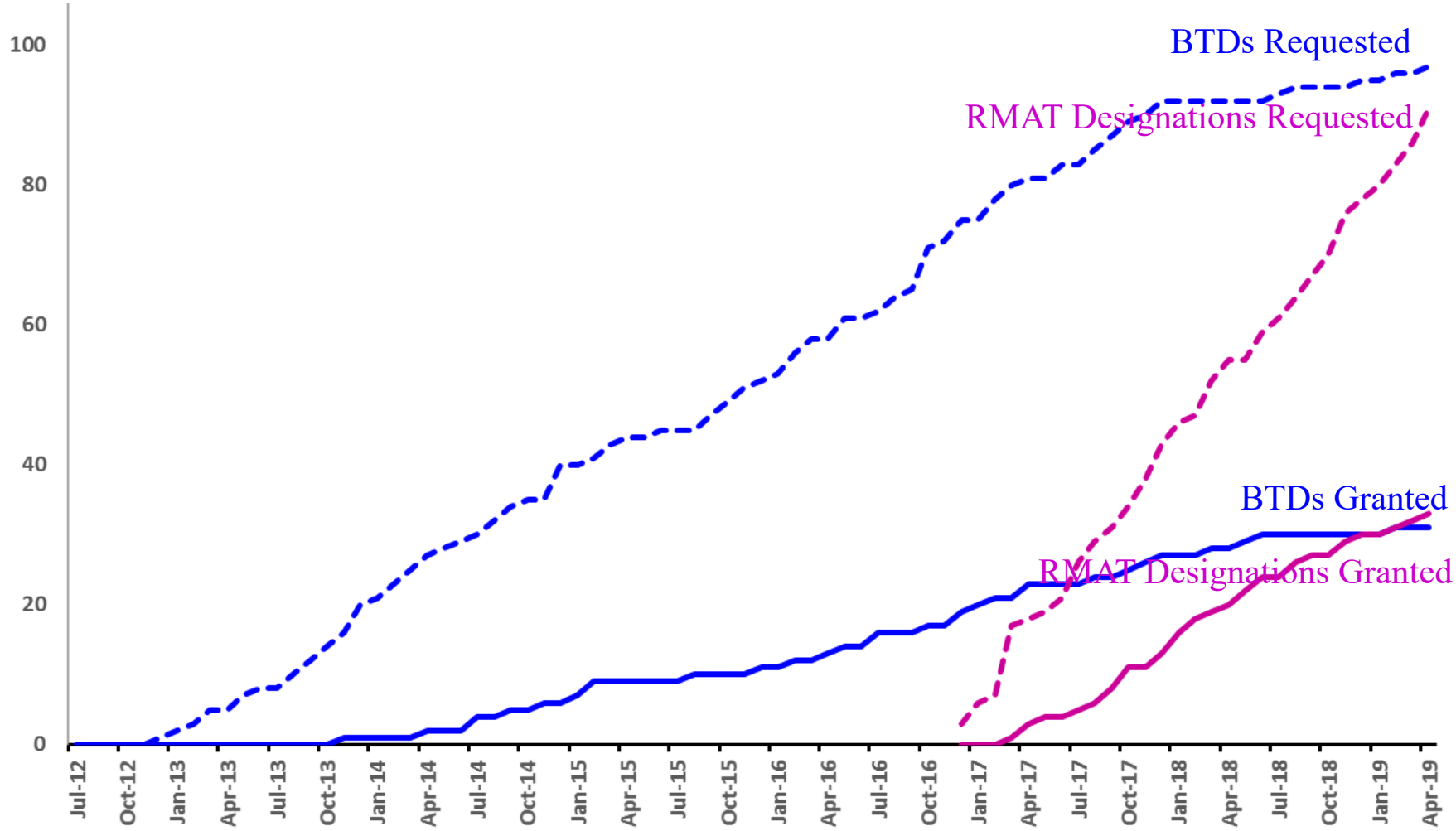


- Cell Therapy Product - Autologous Cells
- Cell Therapy Product - Allogeneic Cells
- Gene Therapy
- Combination and Tissue Engineering

Analysis of Denied RMAT Designation Requests

- Administrative Reasons
  - Inactive IND
  - No preliminary clinical evidence submitted
- CMC Reasons
  - Different product, lack of product comparability data
- Insufficient Preliminary Clinical Evidence
  - Study design issues
  - Inconsistent results with regard to product activity

Cumulative Sum of BTD and RMAT Designation Requests and Granted BTDs and RMAT Designations (through April 13, 2019)



INitial Targeted Engagement for Regulatory Advice on CBER producTs

(previously known as pre-pre-IND interactions)

Applications to FDA

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- Marketing
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Marketing Approval for Drugs and Biologics

- Requirements
  - Substantial evidence of effectiveness
  - Adequate and well-controlled investigations
  - Safety (sufficient to support an overall favorable benefit-risk assessment)

- Types of approval
  - Traditional (aka: standard; regular)
  - Accelerated

Traditional Approval

- Evidence of effectiveness based on an effect on clinically meaningful endpoint(s) (e.g., how a patient feels, functions, or survives)

- No comparative effectiveness requirement (i.e., must be better than no treatment or placebo, but does not need to be better than currently available therapies)

Accelerated Approval (AA)

- Evidence of effectiveness based on an effect on a surrogate endpoint (or intermediate clinical endpoint) that is reasonably likely to predict a drug's clinical benefit
- Treats a serious or life-threatening condition
- Provides a meaningful advantage over existing treatments

Marketing Approval for Drugs and Biologics

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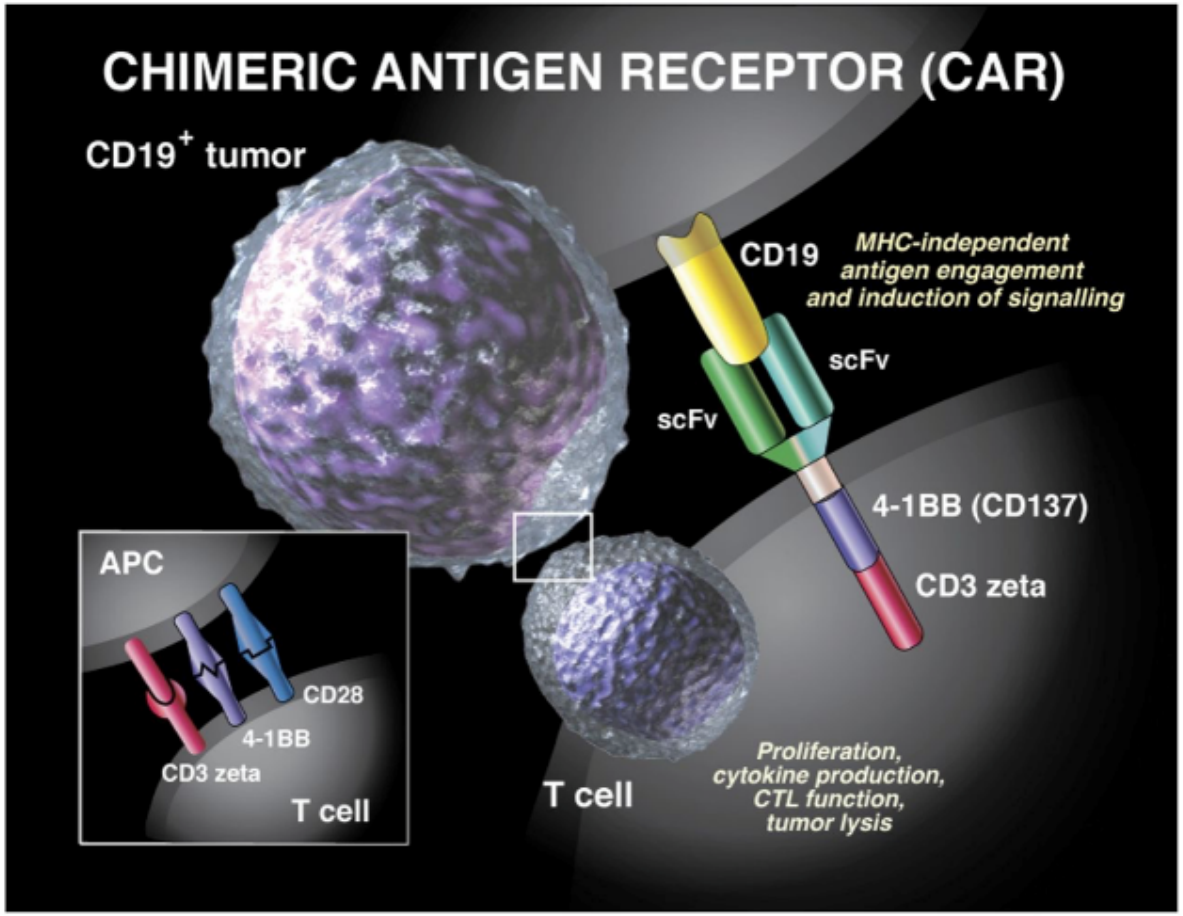
Approved Cell and Gene Therapies

- HPC Cord Blood (multiple banks approved)
- LAVIV (Azficel-T)
- MACI (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane)
- GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen)
- PROVENGE (sipuleucel-T)
- IMLYGIC (talimogene laherparepvec)
- KYMRIAH (tisagenlecleucel)
- YESCARTA (axicabtagene ciloleucel)
- LUXTURNA (voretigene neparvovec-rzyl)

https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/default.htm

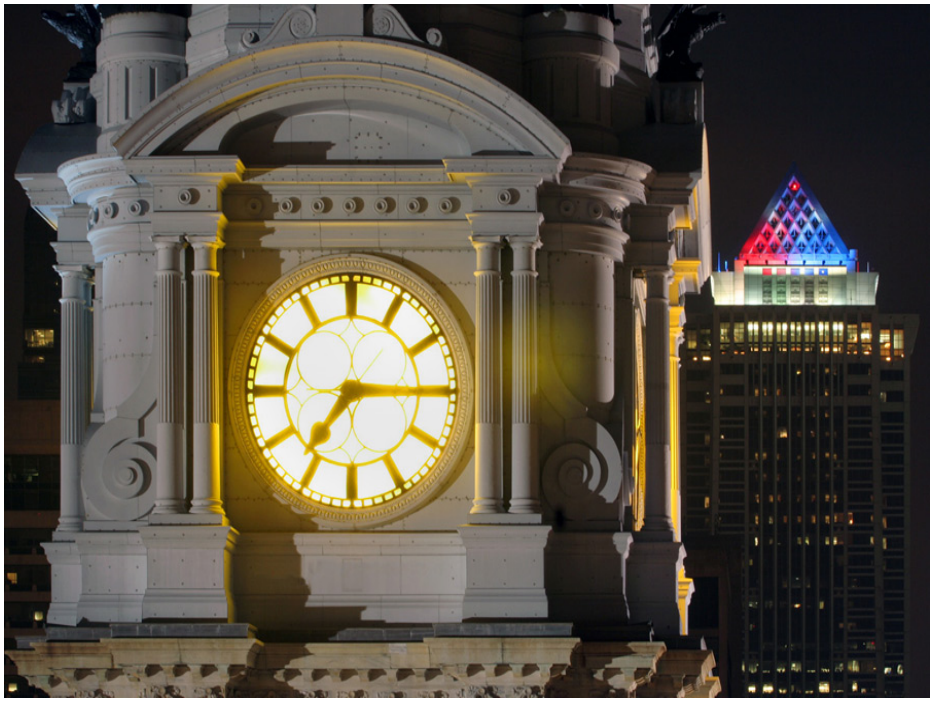
CAR T Cells: A Novel Way to Treat Cancer



Shannon L. Maude et al. Blood 2015

CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex

Philadelphia City Hall



Current OTAT Vacancies: 43

Cell and Gene Therapy (CMC)	12
Clinical Evaluation and Pharmacology / Toxicology	20
Regulatory Project Management	7
Human Tissues	2
Plasma Protein Therapeutics	0
Immediate Office of Director	2

Acknowledgements

- Rachael Anatol, PhD
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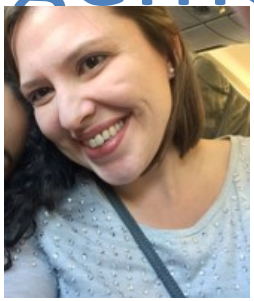
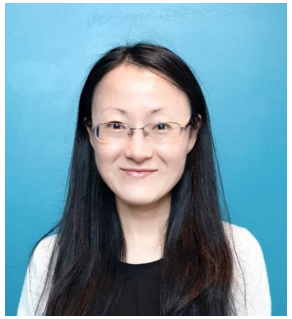
- Xiaofei Wang, PhD



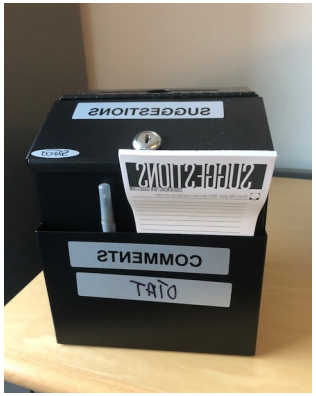


Contact Information

Wilson W. Bryan, M.D.

wilson.bryan@fda.hhs.gov



Contact Information

- **Regulatory Questions:**

  OTAT Main Line – 240 402 8190

  Email: OTATRPMS@fda.hhs.gov and

  Lori.Tull@fda.hhs.gov

FDA Headquarters

- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov

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