FDA Pilot Project to Develop a Clinical Database to Examine Safety in Trials Using CAR T-cells

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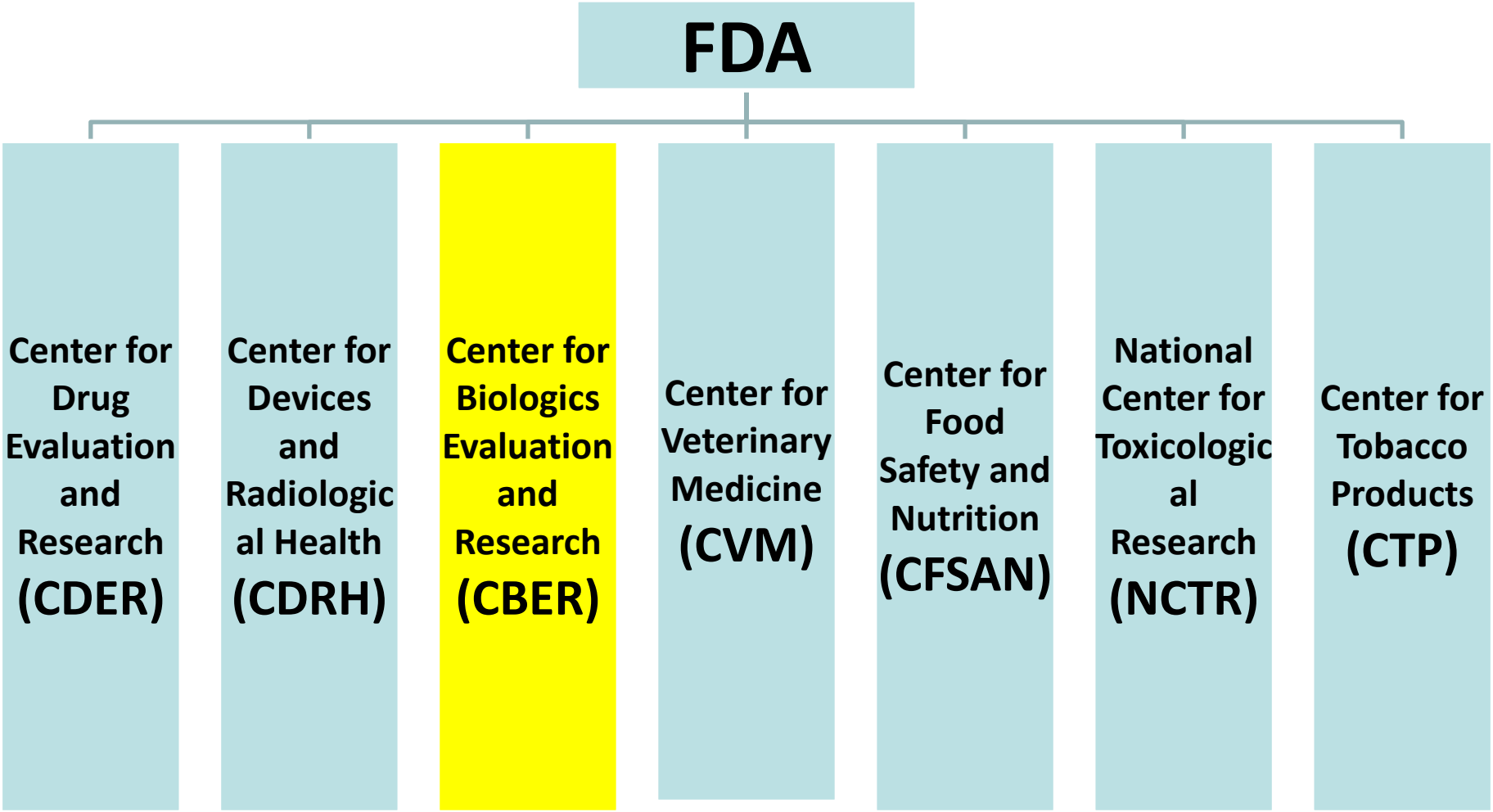
Outline

- Brief Overview of CBER, Office of Tissues and Advanced Therapies (OTAT)
- IND Submissions to OTAT (formerly OCTGT)
  - Engineered T cells: CAR T cells, TCR T cells
- CAR T cell Safety Project
  - Serious adverse events with CAR T-cells
  - Documentation of events
  - Assessment on reviewer and Branch Level
  - Clinical Safety Database Pilot Project

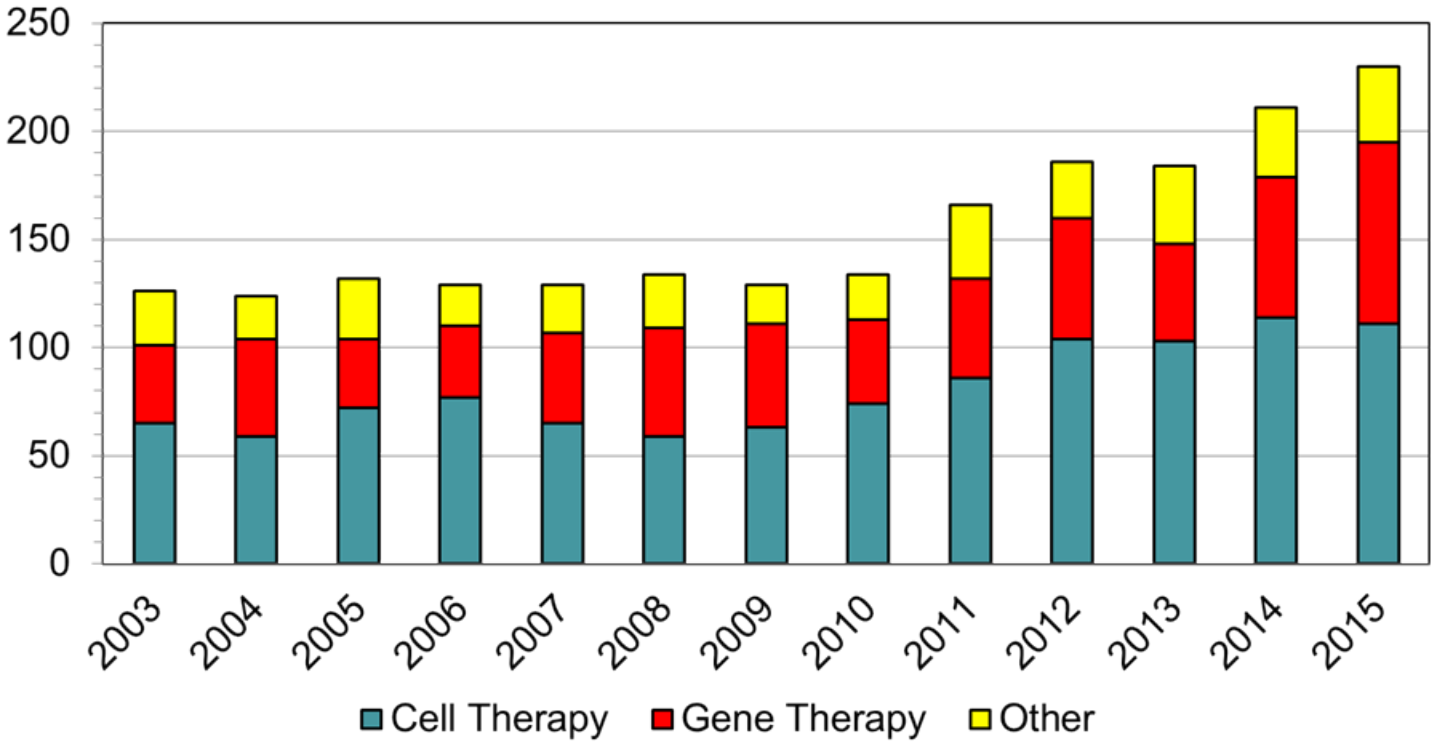
FDA Organization



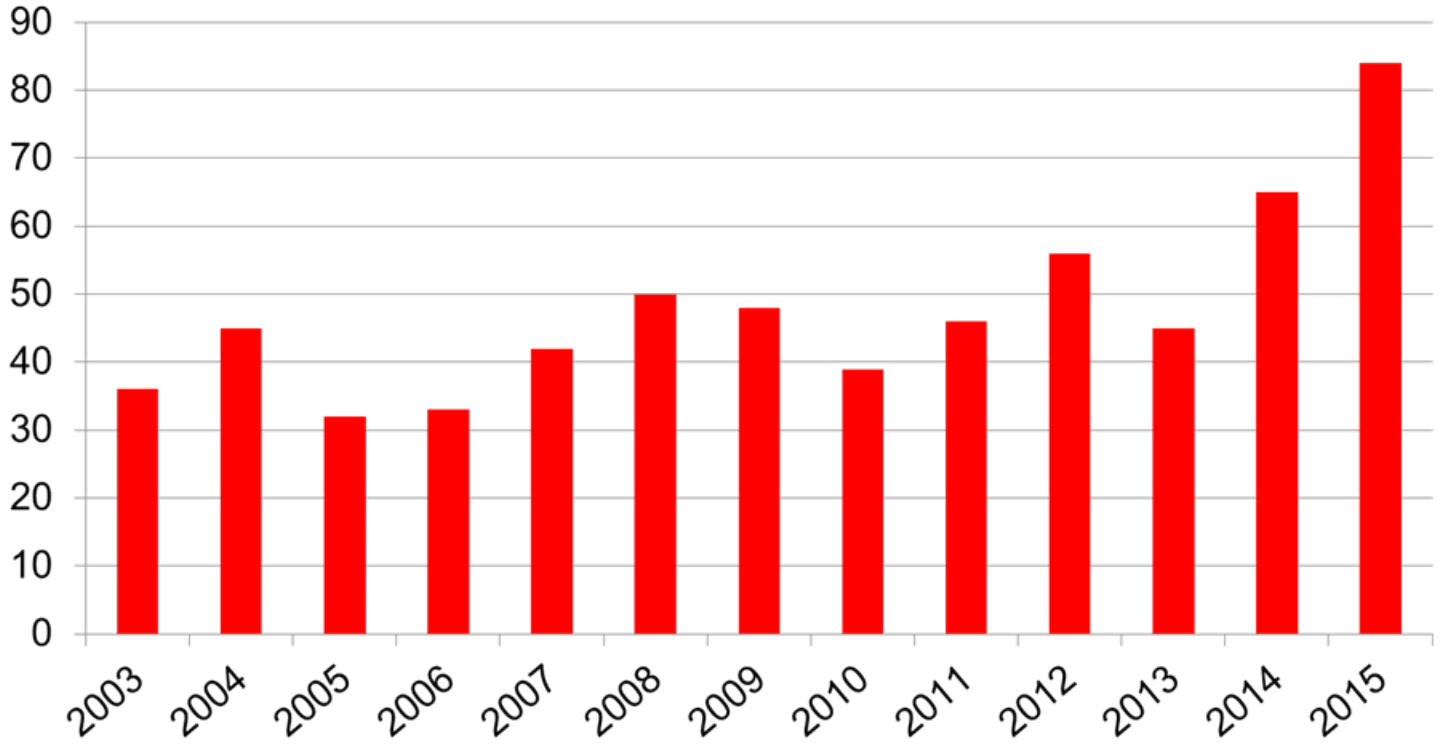
CBER: Center for Biologics Evaluation and Research

OBRR	OVRR	OTAT
Div. of Blood Components and Devices	Div. Of Bacterial, Parasitic, and Allergenic Products	**Div. Of Clinical Evaluation and Pharm/Tox** **Pharmacology/Toxicology 1, 2** **Oncology** **General Medicine 1, 2** **Clinical Hematology**
Div. of Emerging and Transfusion, Transmitted Disease	Div. Of Vaccines and Related Product Applications	**Div. Of Human Tissues** **Div. Of Cellular and Gene Therapies**
	Div. Of Viral Products	**Division of Plasma Protein Therapeutics** **Division of Regulatory Project Management**

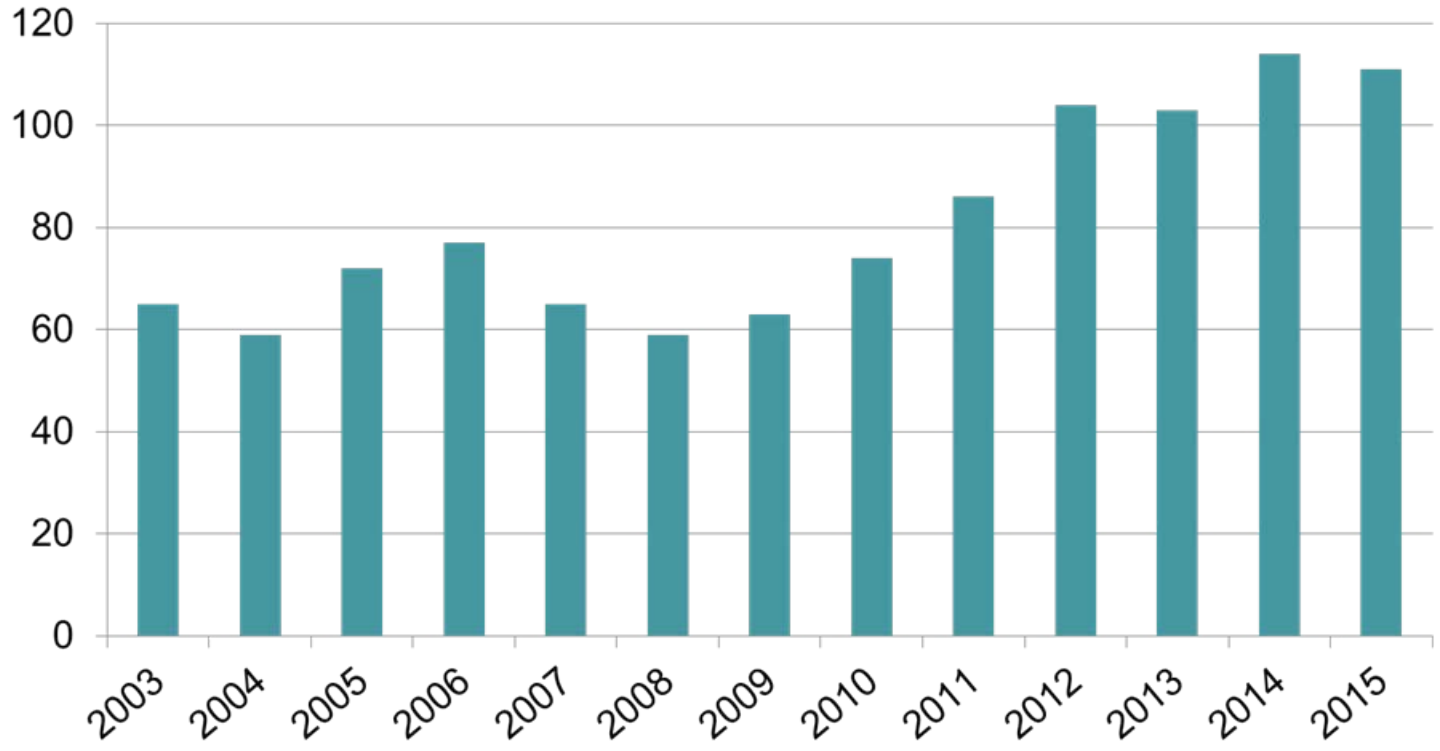
Yearly New IND & IDE Submissions to OCTGT



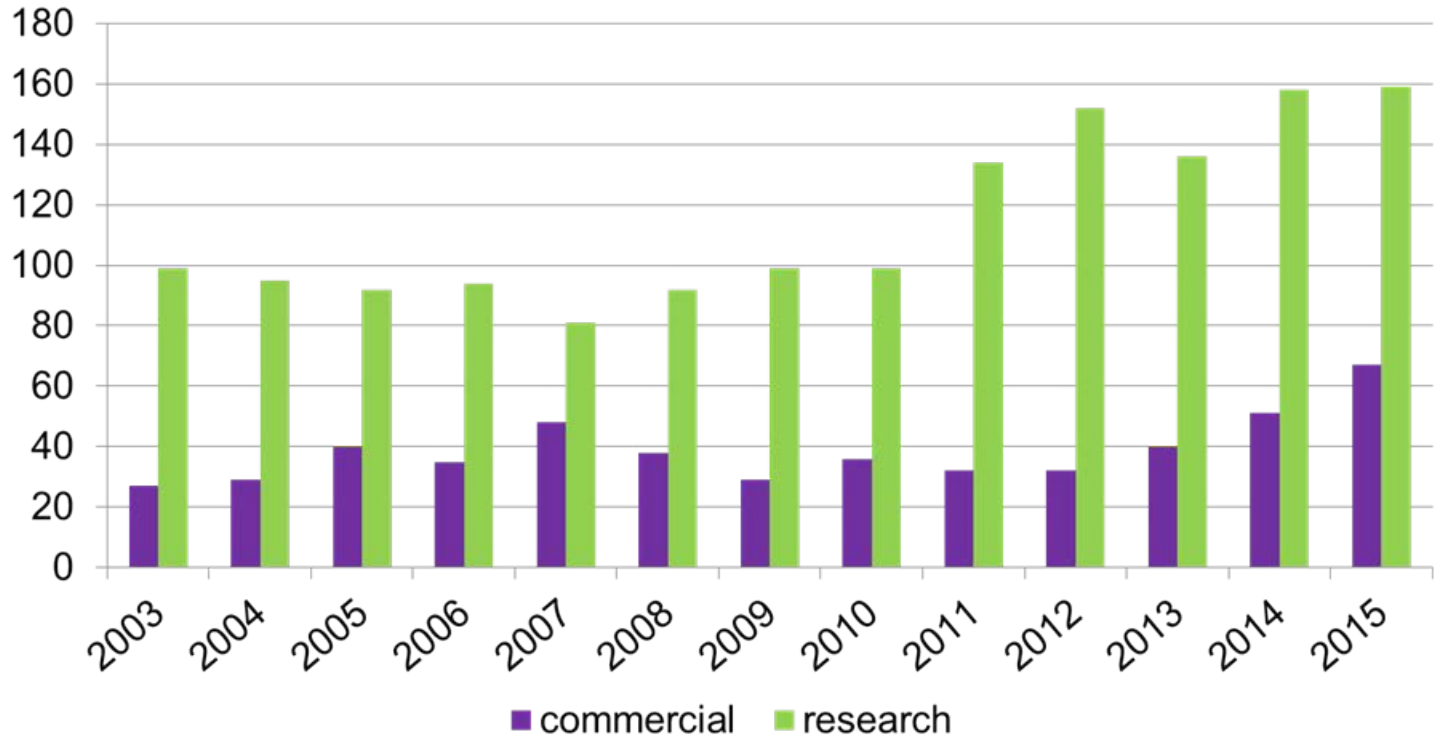
Yearly New Gene Therapy IND Submissions to OCTGT

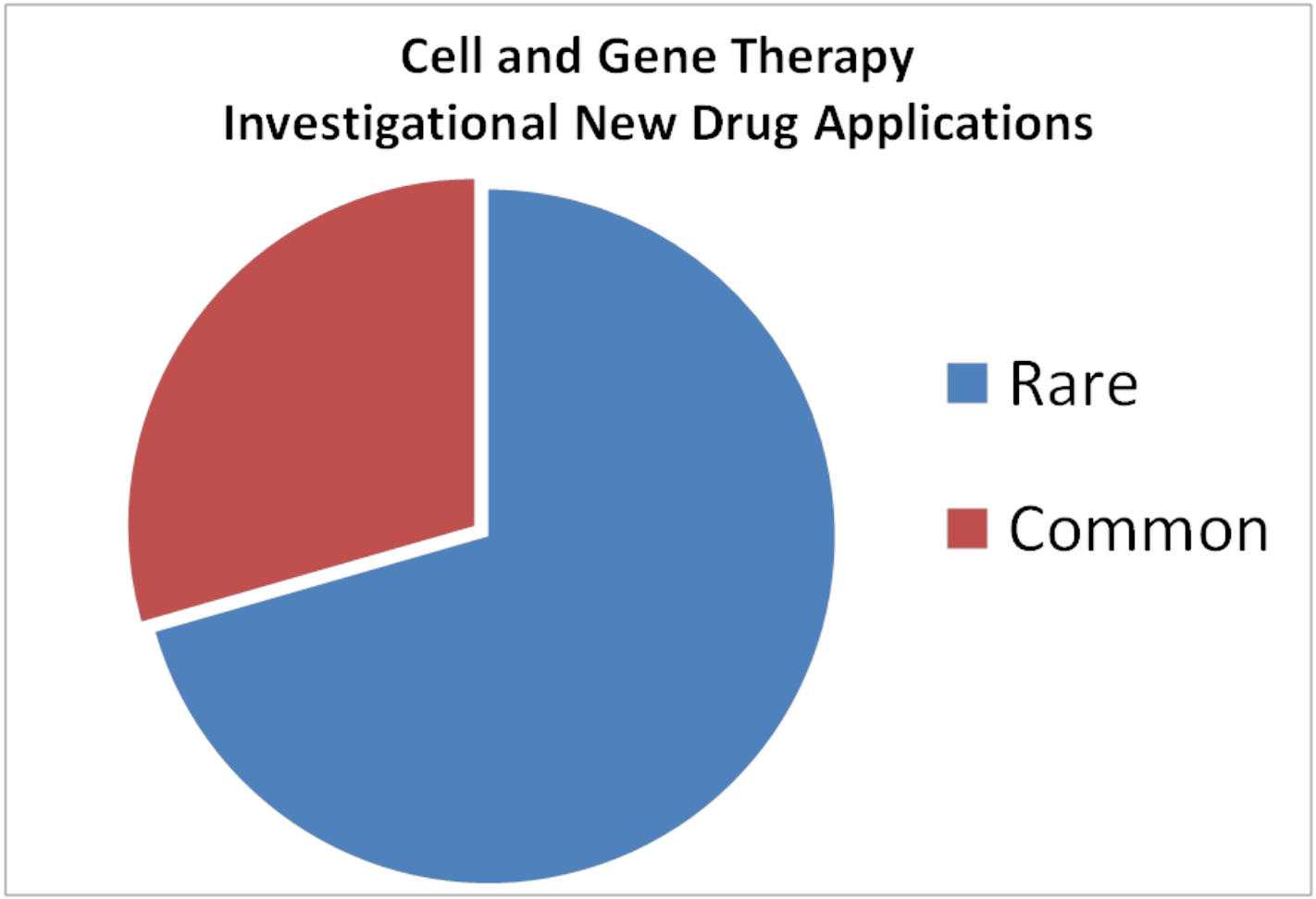


Yearly New Cell Therapy IND & IDE Submissions to OCTGT



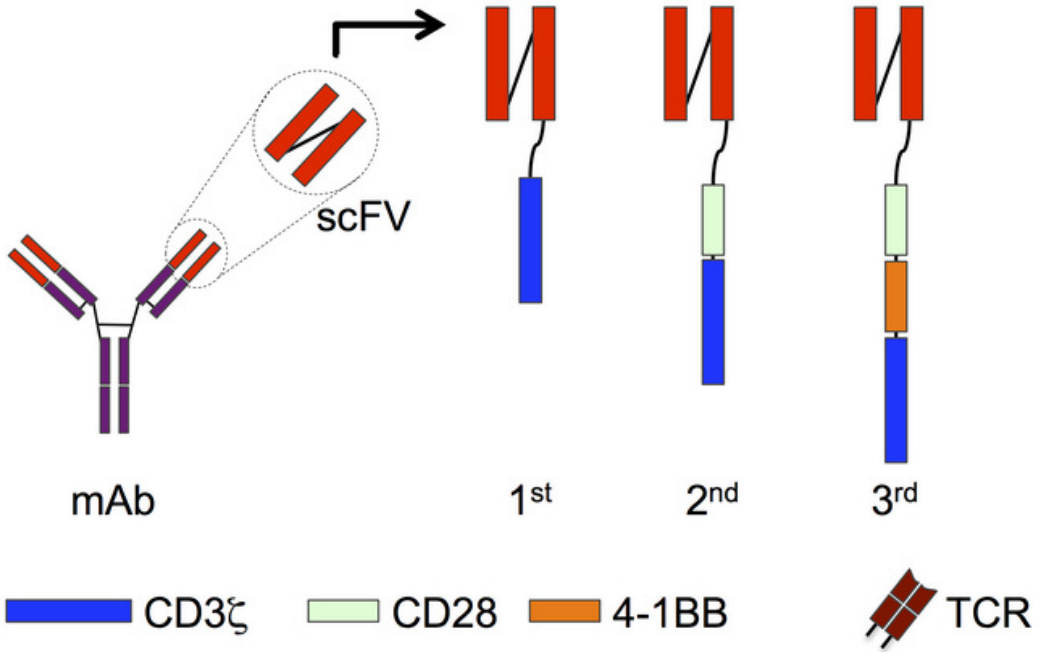
New INDs and IDEs Submitted to OCTGT: Commercial or Research Sponsors

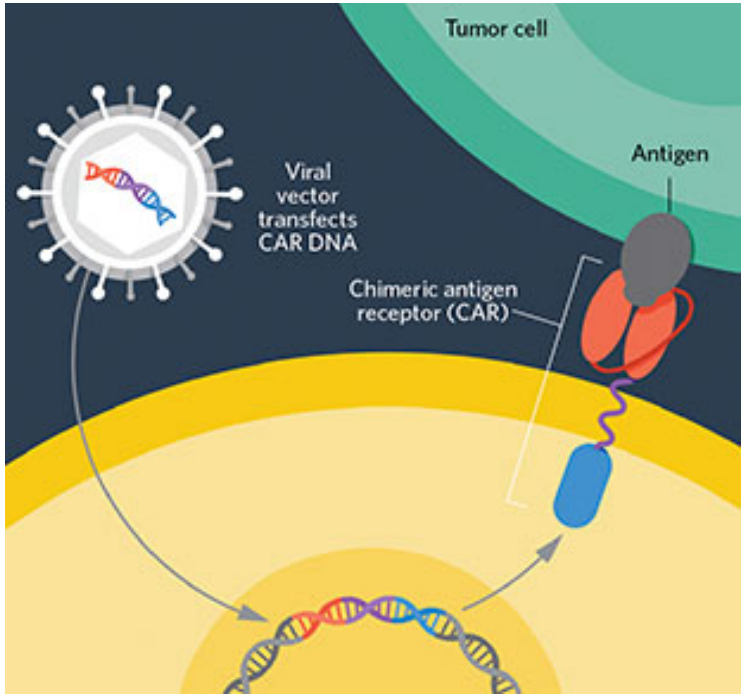



Cell and Gene Therapy
Investigational New Drug Applications
Rare
Common

Chimeric Antigen Receptor (CAR) T-cells

Anti-CD19 CAR T-cell: Anti-CD19 binding domain fused to intracellular T-cell signaling domains; targets B-cells





Michael S. Magee and Adam E. Snook, *Discovery Medicine*, Volume 18, Number 100, November 2014; Vicki Brower, The Scientist, April 1, 2015

T-Cell Receptor / CAR T-Cell INDs

N	
116	Engineered T-Cell: TCRs / CAR T-cells
37	CD19 INDs
16	CD 19 sponsors
1135	Subjects (CD19)

November 1, 2016

IND Submissions to CBER

- Products that are regulated by OTAT
- Definition of a biologic product: Section 351(i) of the Public Health Service Act (42U.S.C. 262 (i))
  - Cell Therapy (CT)
  - Gene Therapy (GT)
  - Combination products
  - Therapeutic vaccines
- Address Unmet Medical Needs
- Personalized/Targeted Therapies

Background on CGT Products

- Design of clinical trials differs from other pharmaceutical products
- Early experiences: CGT may pose substantial risks to subjects
  - Many first-in-human products, unknown safety profile
  - Late-onset T-cell leukemia
- Potential for prolonged biological activity
  - Engineered T cells have the potential to persist for weeks to years
- High potential for immunogenicity

Clinical Trial Design

- Cell and Gene Therapy Products
  - Often lack of clinical experience
  - Need to always consider persistence with cell products
    - Cells- how long detected
  - Manufacturing Timeline: auto and allo cell products
    - Can take weeks to months to produce

Clinical Trial Design

Characteristics of Gene Therapy Products:

- **Delivered gene may be uncontrolled and interfere with normal function**
- **T-cell receptor (TCR) and CAR T-cells**
    - **Off-tumor, on-target**
    - **B-cell aplasia with CAR CD19 products**
    - **Cross-reactivity (Mage A3: titan in the heart and Mage A12 in CNS)**
    - **Unique safety issues**

Summary

- **CBER products, in particular OTAT products, are often unique**
- **We encourage interaction with OTAT prior to IND submission with a PreIND Meeting**
- **We have FDA Guidances and Webinars to help with product development**
- **Novel products and therefore have safety, feasibility, and follow-up that are different than for other therapeutic products**

Maude et al: N Engl J Med (2014) 371: 1507-1518

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

Kochenderfer JN et al: J Clin Oncol (2015) 33:540-549.

VOLUME 33 · NUMBER 6 · FEBRUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor

James N. Kochenderfer, Mark E. Dudley, Sadik H. Kassim, Robert P.T. Somerville, Robert O. Carpenter, Maryalice Stetler-Stevenson, James C. Yang, Giao Q. Phan, Marybeth S. Hughes, Richard M. Sherry, Mark Raffeld, Steven Feldman, Lily Lu, Yong F. Li, Lien T. Ngo, Andre Goy, Tatyana Feldman, David E. Spaner, Michael L. Wang, Clara C. Chen, Sarah M. Kranick, Avindra Nath, Debbie-Ann N. Nathan, Kathleen E. Morton, Mary Ann Toomey, and Steven A. Rosenberg

The New York Times

T-Cell Therapy Puts Leukemia Patients in Extended Remission

OCT. 15, 2014

CBS NEWS

CANCER BREAKTHROUGH: PROMISING TREATMENT USES PATIENT'S OWN IMMUNE SYSTEM TO ATTACK DISEASED CELLS

FEBRUARY 20, 2014

Safety Concerns

Reported Deaths with CAR T-cells

- **Cytokine Release Syndrome (CRS)**
  - **Complex reaction with multiple components**
  - **Renal and cardiac complications**
  - **Is there a benefit to CRS?**
- **Cardiac events +/- CRS**
- **Neurologic deterioration +/- CRS**
- **Infections**
- **Intracranial hemorrhage**
- **Prolonged aplasia**

Safety Concerns (continued)

- On-target, Off-tumor toxicity
  - T-cell receptor (TCR) example of MAGE A3
    - Cardiac
    - Neurologic

- Long-Term Toxicity issues
  - Persistence of CAR T-cells
  - B-cell aplasia with antiCD19 CAR T-cells
  - Unknown risk for insertional oncogenesis, replication competent retrovirus (RCR)
  - Potential for second malignancy

Documentation of Events

- **Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and Bioavailability and Bioequivalence (BA/BE) Studies (December 2012)**
  - **Mandatory reporting of suspected unexpected safety adverse reactions (SUSARs)**
  - **MedWatch format**
  - **Review is incident by incident**
  - **> 116 INDs with engineered T-cells**
  - **Office-wide review system developed**
    - **CAR T-cell Working Group**
  - **Need a systematic approach to safety across INDs**

Project Objectives

- **To assess the feasibility of systematically collecting, storing and analyzing safety data from CAR T cell products in a way that enables cross-study / cross-IND analysis.**

- **To develop prediction models that can identify safety issues associated with CAR T cell products, leading to the development of risk mitigation strategies.**

Choice of antiCD19 CAR T-cell Products

- Potential to be curative
- Complex *in-vivo* activity
- Substantial & complex safety concerns
- Complex manufacturing processes that relate to clinical safety issues
- Relatively large number of anti-CD19 CAR T-cell INDs, but small number of subjects in each IND
- Ongoing Phase 3 studies

Safety Concerns
Cytokine Release Syndrome (CRS)
Neurologic Complications
Intracranial Hemorrhage
Potential for Second malignancy

Pilot CAR T-Cell Databases

Two databases:

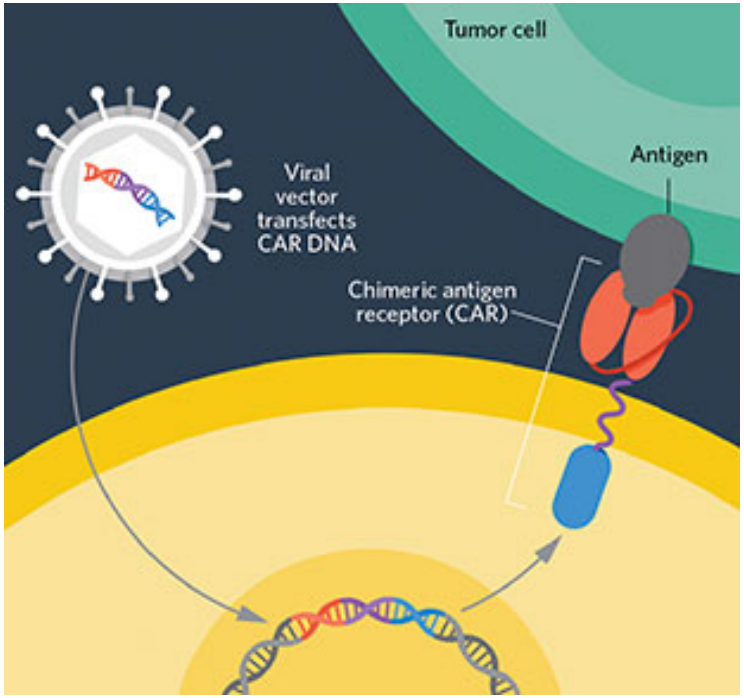
- **Clinical Safety Database**
  - **Will use CDISC – SDTM format for data submission to facilitate submission of clinical and safety information from CAR T-cell INDs or other similar electronic formats**
- **Chemistry, Manufacturing, and Control (CMC)**
  - **Information from INDs and additional Sponsor inquiries**

Pilot Clinical Safety Project

- Interactive process between Sponsor and FDA
  - Companies/research institutions are likely to already have safety data bases; or else it would be easy for them to compile the data
  - Ask that data be submitted earlier in the process of product development
- Sponsor-specific data available through IND safety reporting process
- Flexible about data formats

CMC CAR T-cell Project

- Cross-IND analysis
- Most of the data already submitted to the INDs with CMC submissions
- Inform regulatory review of CAR T-cell product development
- Relationship between product class attributes and clinical safety



Why Does the FDA Need This Safety Database?

Integrate and analyze safety data for this product class

- **Understand the complex relationships of clinical (e.g., dose) & manufacturing factors to safety**
- **Small study sizes make risk assessments difficult**
- **Existing system of data collection is cumbersome**
- **Data formats are complex and variable**
- **To better inform sponsors of safety concerns for a particular product class**

Why Does the FDA Need This Safety Database? (continued)

FDA can analyze across INDs from multiple sponsors

- **IND sponsors are often unwilling to share information with each other**
- **No data-sharing limitations within the FDA**
- **FDA can maintain strict confidentiality of proprietary information**

Pilot Project Requirements

Efficient data analysis requires:

- **Collection of clinical and manufacturing data in a standardized manner**
- **Systematic organization of clinical and manufacturing data in databases**
- **Scientific computing to perform the data analysis**

HIVE Database: High performance Integrated Virtual Environment

HIVE is the database for the clinical safety information

- **A database that is optimized for the storage, retrieval, and analysis of large amounts of data, so it is an ideal environment for developing the CAR T-cell database.**
- **Enables FDA to capture the complex structure and relationships found in clinical and manufacturing data.**
- **Pre-existing at FDA**

Clinical Safety Project

These analyses will provide safety information to allow for knowledge-based advice for the CAR T-cell products

- **For future analysis of serious adverse events, as well as overall safety analysis for these products, FDA can expand beyond single-episode / single-IND evaluation of severe adverse events to allow for more consistent review of safety concerns**
- **For the sponsor, FDA can provide more reliable advice regarding product development**
- **May be applicable to other product classes under development.**

Pilot Project Phases

- **Phase 1: Collection of data in a standardized manner using existing format.**

- **Phase 2: Store data in FDA database (HIVE) using an integrated data format, which will enable fast cross-study/cross-IND data queries.**

- **Phase 3: Conduct cross-study/cross-IND analysis of data retrieved from HIVE.**

Phases can overlap and are not sequential.

National Institutes of Health Recombinant DNA Advisory Committee Presentation:

Points of discussion:

- **Amount of Data Needed**
  - **Unknown, exploratory pilot project**
- **Preserving Confidentiality**
  - **FDA routinely evaluates individual safety issues and maintains confidentiality**
  - **Findings will be presented as class-specific advice to sponsors**
- **Sponsor Burden**
  - **Data requested is already being collected**
  - **Not expecting pristine data**

Testing Tasks Performed: Data Analysis / Modeling

- Developed preliminary models based on analyses requested by the clinical team.
- Developed data visualization tools that can be used in HIVE.
- Developed models to improve sensitivity of classification models.
- Explored tools for developing predictive models
- Current Test Analysis on early dataset from CD19 CAR T cell products
  - Effects of CRS management treatment on CRS outcomes
  - Effects of treatment dose on toxicity
  - Effects of treatment dose on cytokine levels

Pilot Data Safety Project: Summary

- Viability of this project depends on participation of sponsors
- FDA is in the testing phase
- Once this testing is complete, FDA will ask additional sponsors to provide the clinical data previously collected through IND safety reporting
- FDA is aware that data collected on these trials so far may be incomplete; however, if this information is submitted, it will add to the strength of the database

Thank you

- **CAR T-cell Safety Project**
- **T-cell working Group**

Chimeric Antigen Receptor (CAR) T-Cell Project Team

- OTAT
  - Kristin Baird, MD
  - Wilson Bryan, MD
  - Denise Gavin, PhD
  - Bindu George, MD
  - Xiaobin Lu, PhD
  - Maura O'Leary, MD
  - Kim Schultz, PhD
  - Robert Sokolic, MD
- OBE
  - John Scott, PhD
- High-Performance Integrated Virtual Environment (HIVE)
  - Vahan Simonyan, PhD
  - Alin Voskanian-Kordi
- ENGILITY
  - Judith Crumpler
  - Thomas Heiman, PhD
  - Yonatan Negash

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OTAT T-Cell Working Group

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  or Lori.Tull@fda.hhs.gov
- References for the regulatory process for OCTGT
  - http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation
  - OCTGT Learn Webinar Series:
    http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

Public Access to CBER

CBER website:
http://www.fda.gov/BiologicsBloodVaccines/default.htm
Phone: 1-800-835-4709

Consumer Affairs Branch (CAB)
Email: ocod@fda.hhs.gov

Manufacturers Assistance & Technical Training Branch (MATTB)
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