What's New in CBER?

Childhood Cancer Advocacy Forum

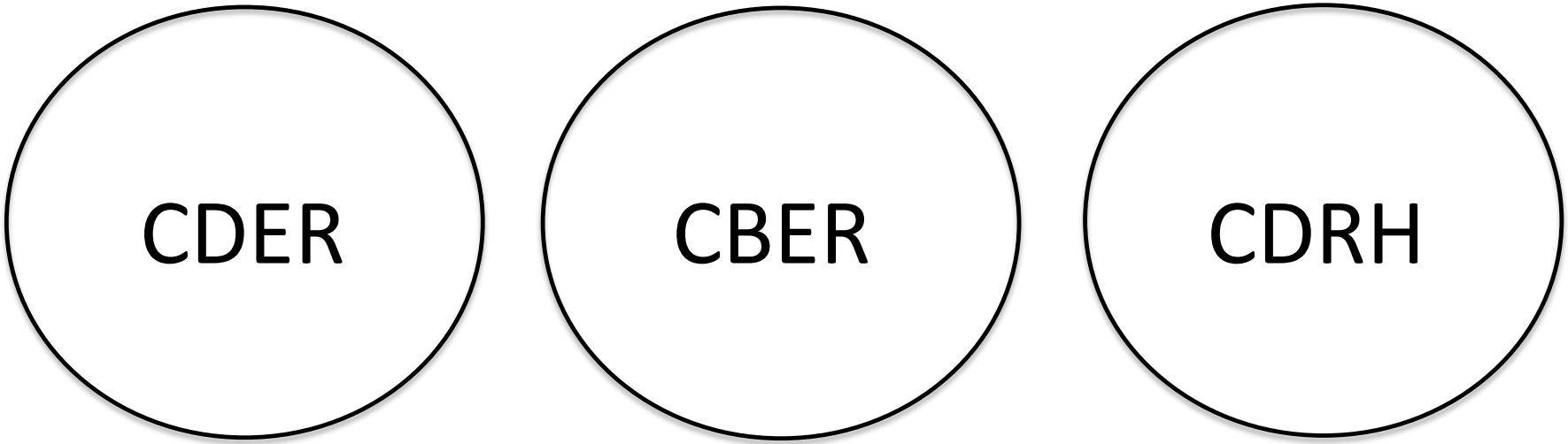
March 15, 2019

Megha Kaushal, MD
Medical Reviewer, Clinical Hematology Branch

Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
United States Food and Drug Administration

FDA Regulation of Oncology Products

Oncology Center of Excellence (OCE)



Drugs (small molecules)

Biologics

- Monoclonal Antibodies
- Therapeutic Proteins
- Cytokines

Cell therapies

Gene Therapies

Oncolytic viruses

Therapeutic vaccines and immunotherapies

Companion Diagnostics

Devices

Office of Tissues and Advanced Therapies

- Cellular Therapies (non-immunotherapy)
- Immunotherapies
  - Cell therapies
  - Therapeutic Vaccines
- Gene Therapies
  - Gene transfer into cancer cells to induce cell death
- Oncolytic viruses
  - Viruses that are engineered to target and destroy cancer cells while not harming the rest of the body

Office of Tissues and Advanced Therapies

- Approximately 1000 active IND/IDE
- 75% are research/academic Sponsors
- 3 approved oncology cell, gene or vaccine products
- 5-10% have active pediatric trials
- The field of cell and gene therapy is relatively new
  - Unique known and unknown risks, particularly for pediatric patients

FDA

The New York Times (OCT. 15, 2014)
Cell Therapy Puts Leukemia Patients in Extended Remission

The Washington Post

Aug 30, 2017

FDA clears first gene-altering therapy — 'a living drug' — for childhood leukemia

Oct 18, 2017

US regulators approve 2nd gene therapy for blood cancer

What is Chimeric Antigen Receptor (CAR) T Cell Therapy?

- Novel type of cancer immunotherapy
- Involves training patients' own immune cells (T cells) to attack cancer cells

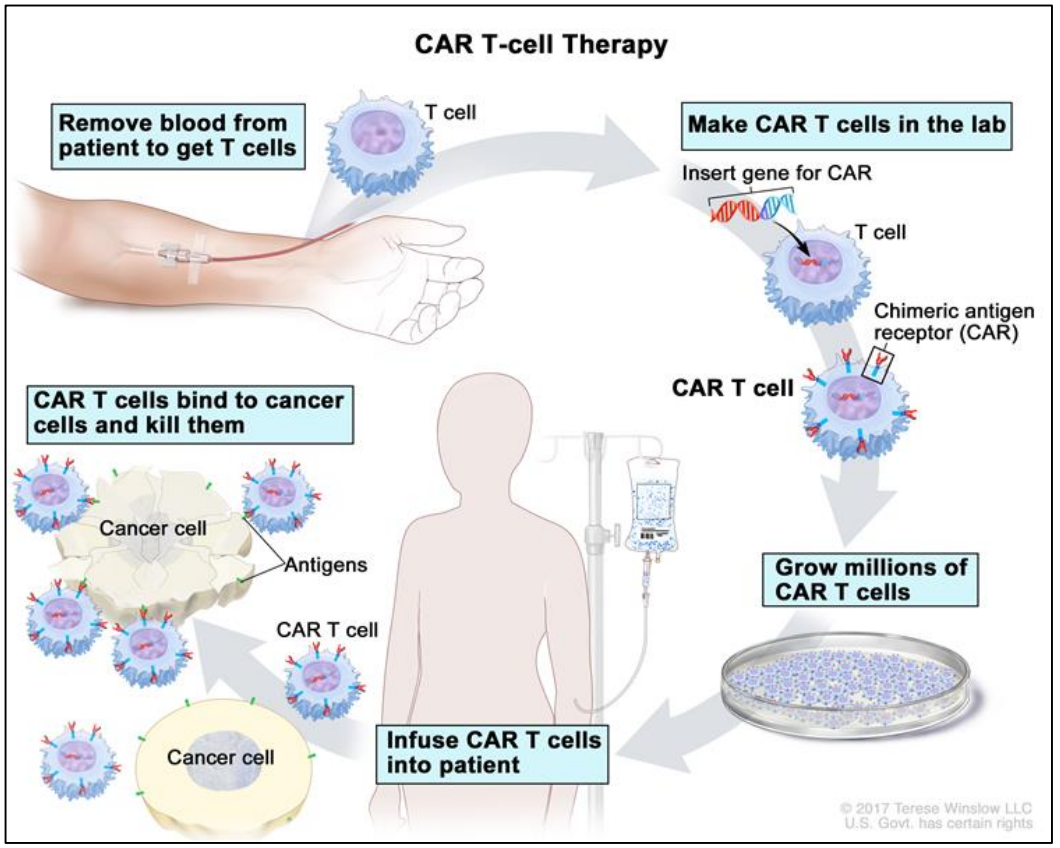
The Washington Post

Emily Whitehead, shown with her parents, was the first child treated with CAR T cell therapy

Chimeric Antigen Receptor T-cells (CAR T-cells)

Making CAR-modified T cells

- Patients undergo a procedure (apheresis) for T-cell collection.
- A modified virus (viral vector) is used to infect the T-cells and transfer new genetic material into the CAR T-cell.
- CAR T-cells undergo culture for growth, expansion and activation outside of the body.
- Patients typically receive lymphodepleting chemotherapy prior to T-cell infusion.



https://www.cancer.gov

CAR-T Gene Therapy Marketing Approvals in 2017

- **Kymriah** (tisagenlecleucel)
  - CAR-T cells (target – CD19)
  - Refractory childhood lymphoblastic B cell leukemia
  - Novartis

  https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=368

- **Yescarta** (axicabtagene ciloleucel)
  - CAR-T cells (target – CD19)
  - Refractory adult patients with relapsed or refractory large B cell lymphoma
  - Gilead (Kite)

  https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=375

Efficacy

- Single arm study
- Approval was based on:
  - Overall Response Rate (ORR)= Complete Response (CR) + Partial Response (CR)
  - Duration of response
- Pediatric and young adult leukemia
  - CR = 63%

CAR T Cell Therapy Can Cause Severe Side Effects

- Side effects can be fatal or life-threatening
- Majority of patients experienced:
  - **Cytokine Release Syndrome (CRS)**:
    - Systemic response to T-cell activation: flu-like symptoms, difficulty breathing, body organ toxicities
    - FDA expanded the approval of Actemra (tocilizumab) to treat CRS
  - **Neurologic toxicities**:
    - Confusion, inability to talk, seizures, brain swelling

FDA's Measures To Reduce The Risks of CAR T Cell Products

- Boxed warning for CRS and neurologic toxicities
- Approval with a Risk Evaluation and Mitigation Strategy (**REMS**)
  - To ensure the benefits of the drug outweigh the risks
  - Protective measures in place to ensure patients' safety:
    - Hospitals must be certified
    - Education of physicians, hospital staff and patients about the recognition and management of CRS and neurologic toxicity

Long-Term Safety Concerns

- Theoretical risk:
  - Secondary malignancies
- Post-marketing requirement (PMR)*:
  - Observational study to collect safety and survival information
  - 15 year follow-up for known and anticipated adverse reactions

*Note: post marketing requirements (PMRs) are distinct from REMS programs

What's next?

- Is CAR T therapy a bridge to Transplant?
- Bi-specific CAR-Ts for Leukemia (targets for naïve or resistant CD19 CAR immunotherapy)
- CAR T cells for solid tumors

CAR T-cell for Solid Tumors

- Approximately 15 solid tumor CAR T-cell trials open to pediatric enrollment listed on ClinicalTrials.gov
- Limited data published so far, but some activity reported in glioblastoma and neuroblastoma
- Area of intense research interest

CAR T-cell for Solid Tumors

- Challenges
  - Less successful than for hematologic malignancies
  - Target identification, distinguishing from normal tissue
  - Trafficking and homing to tumor site
  - Mediate cytotoxicity despite immunosuppressive environment

Acknowledgements

- Kristin Baird, M.D.
- Najat Bouchkouj, M.D.
- Bindu George, M.D.
- OTAT and OCE

Questions?

Contact Information

- **Megha Kaushal, MD**

  megha.kaushal@fda.hhs.gov
- **Regulatory Questions:**

  OTAT Main Line – 240 402 8190

  Email: OTATRPMS@fda.hhs.gov and

  Lori.Tull@fda.hhs.gov
- **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
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.hhs.gov
- **Follow us on Twitter:** https://www.twitter.com/fdacber

FDA Headquarters


FDA
U.S. FOOD & DRUG
ADMINISTRATION