U.S. FOOD & DRUG ADMINISTRATION

FDA's Efforts to Advance Cell and Gene Therapy

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FDLI Regenerative Medicine Conference

June 8, 2021

Agenda

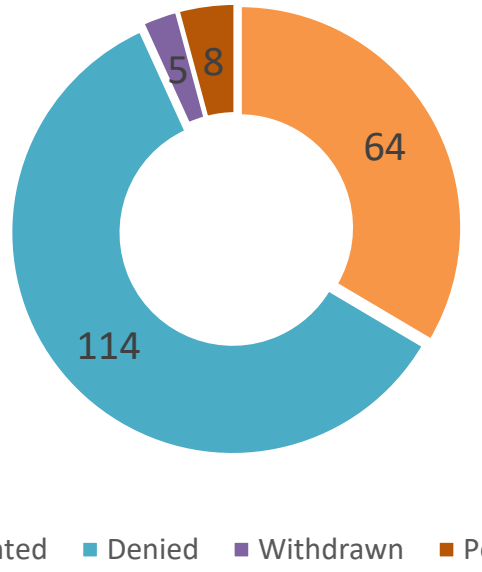
- Summarize recent trends and approvals
- Review genetically-modified cell therapies
- Discuss directly administered gene therapies
- Highlight the importance of very rare diseases
- Suggest areas for focused applied research
- Compare and contrast cell and gene therapies

Impact of COVID-19

- FDA continued to get gene therapy investigational new drug applications through the time of the pandemic
  - Calendar Year 2019 243
  - Calendar Year 2020 237
- Need to individually assess ongoing clinical trials, given interruption of some assessments

Regenerative Medicine Advanced Therapy Designation

191 requests as of May 15, 2021



64 requests granted as of May 15, 2021

FY 2021 Product Approvals

- **Lisocabtagene maraleucel (Breyanzi):** For the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy

  Approved Feb 5, 2021

  https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel

- **Idecabtagene vicleucel (Abecma):** Treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

  Approved March 26, 2021

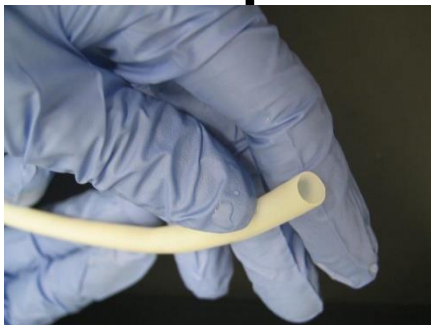
  https://www.fda.gov/vaccines-blood-biologics/abecma-idecabtagene-vicleucel

U.S. Approved Gene Therapies

- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)

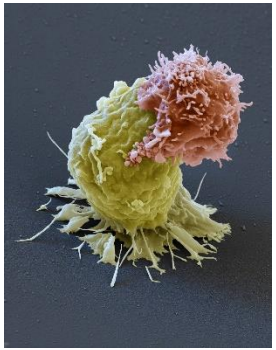
Some Cell-Based Therapies

Bioengineered skin



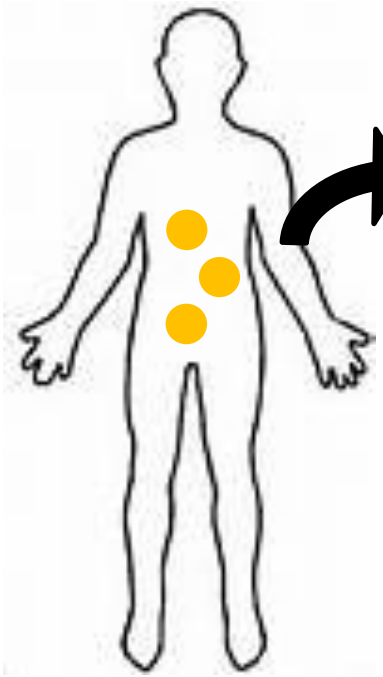
Bioengineered blood vessel

Bioengineered bladder



Chimeric antigen receptor-T cell (in red) attacking a cancer cell (in yellow)

Autologous CAR-T Cell Therapy



Patient

T cell activation and transduction with gene transfer vector (lentivirus)

Apheresis Product

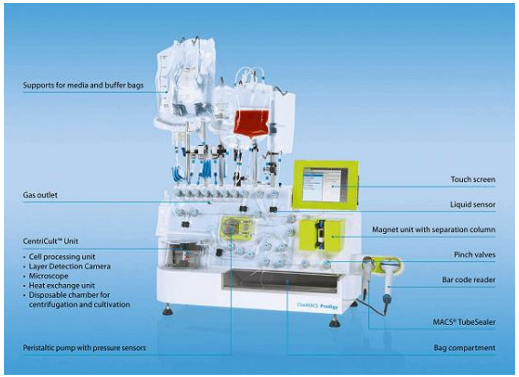
Expand in culture CD3/CD28 beads ± IL-2 / IL-15

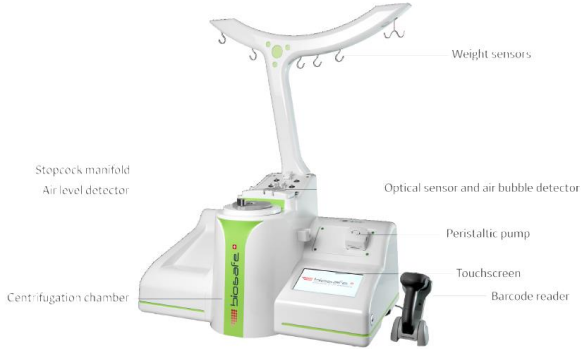
Dose formulation Product testing

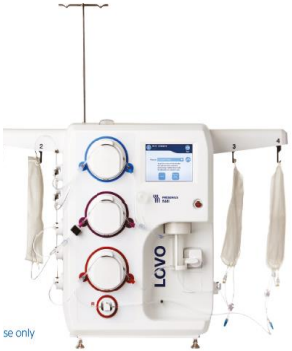
Gene modified T cell Infusion

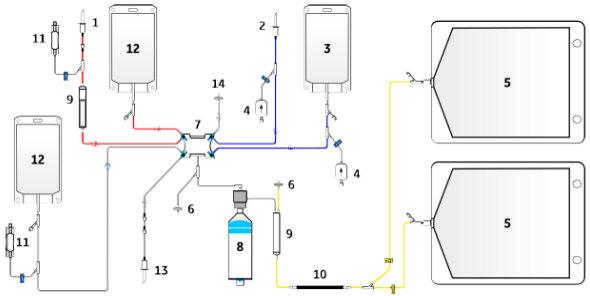
Patient may receive pre-conditioning chemotherapy prior to infusion
Sometimes cytokine support (IL-2) post-infusion

CAR-T Manufacturing Systems









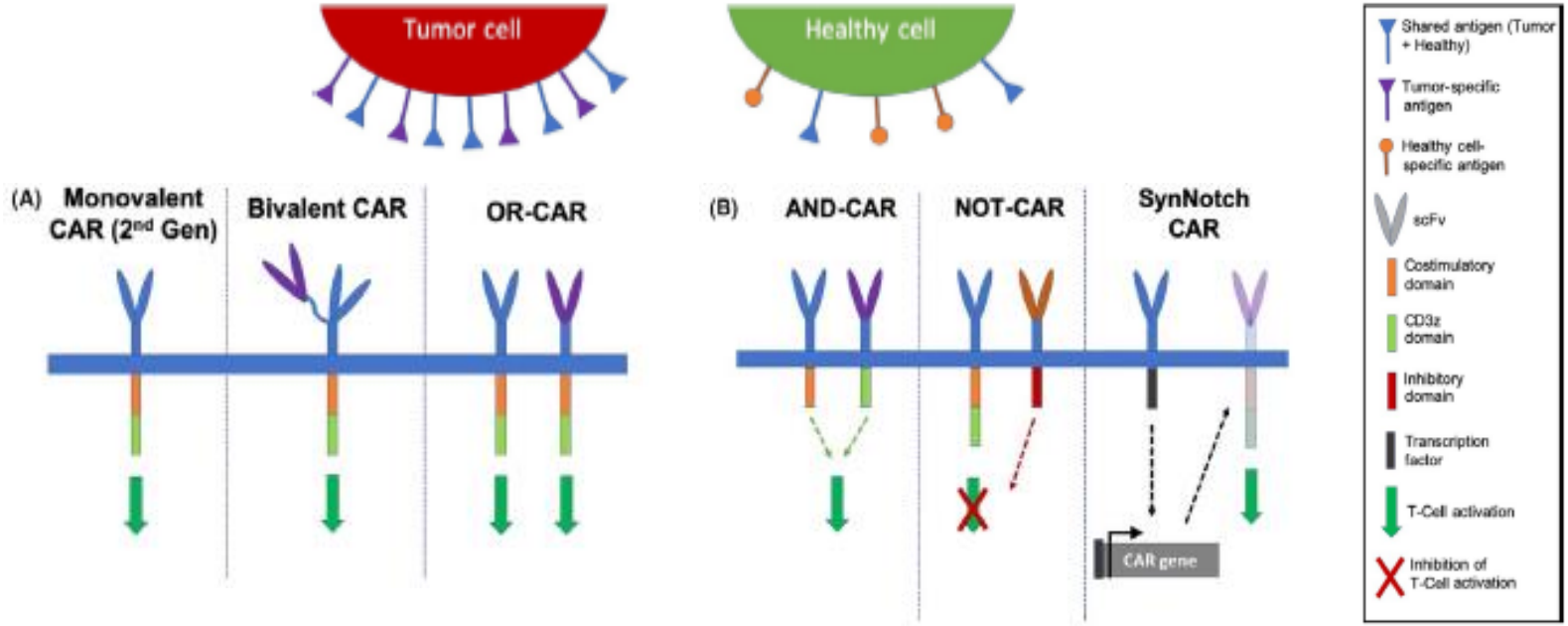
CAR-T Cells for Solid Tumors

- Several challenges have hindered the development of CAR-T cells for solid tumors
  - Targeting of the CAR-T cell to the tumor's location
  - Overcoming immunosuppressive microenvironment
  - Achieving optimal CAR-T cell function over time
  - Relative paucity of highly specific tumor antigens

Allogeneic CAR-T Cells

- Molecular biology, including genome editing, allows the development of cells deficient in MHC class I molecules (multiple methods)
- Potentially facilitates off the shelf product
  - Promotes manufacturing consistency
  - Available immediately for those in need
  - May ultimately reduce cost of therapy

Novel CAR-T Cell Constructs



Broadening Antigen Targeting

Narrowing Antigen Targeting

Adapted from: Walsh Z, Yang Y, Kohler ME. Immunological Reviews 2019;290:100-113

CAR-T Cell Summary

- Autologous CAR-T cells represent the first wave of more effective cell-based immunotherapies
- Further development may lead to
  - CAR-T cell products with reduced toxicity
  - Allogeneic CAR-T products for hematologic use
  - CAR-T cell products effective against solid tumors
  - Uses of CAR-T cells for minimal residual disease

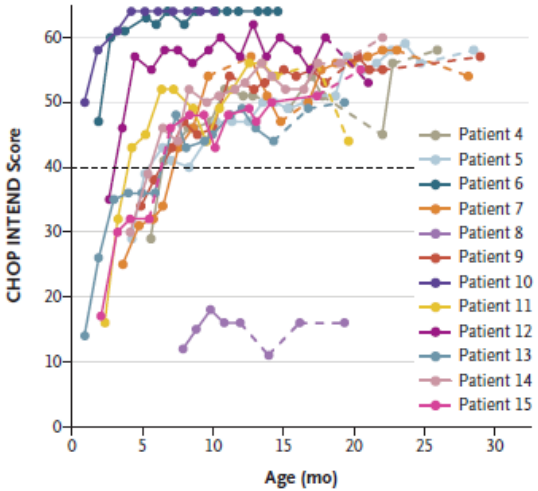
FDA Approved Systemic Directly-Administered Gene Therapy

- **Onasemnogene abeparvovec-xioi (Zolgensma):** for the treatment of patients less than two years of age with spinal muscular atrophy (SMA) with confirmed biallelic mutations in the *survival motor neuron 1* (*SMN1*) gene
  - SMA Type 1 commonly presents with muscle weakness that is evident at birth or within the first few months of life

https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease

Onasemnogene Clinical Results

Clinical trial results: patients with infantile-onset SMA that are untreated do not develop a CHOP INTEND score (a test for neuromuscular disorders) greater than 40



Mendell JR et al. NEJM 2017; 377:1713-1722

Evelyn with documented SMA1 treated with onasemnogene, now age 3 running around, something never seen in untreated children

Importance of Therapies for Disorders that are Very Rare

- Out of thousands of rare hereditary and acquired diseases there are hundreds of disorders affecting one to a few dozen per year that could be addressed with novel therapies
  - Addressing molecular defects may reduce some more common diseases to very rare diseases

Individualized medicine

Creating the right drug to treat the patient

Customized Products

Same indication

Same mode of action

Example:
Personalized vaccine for pancreatic cancer using dendritic cells pulsed with an individualized peptide mixture

Created Products

Different indication

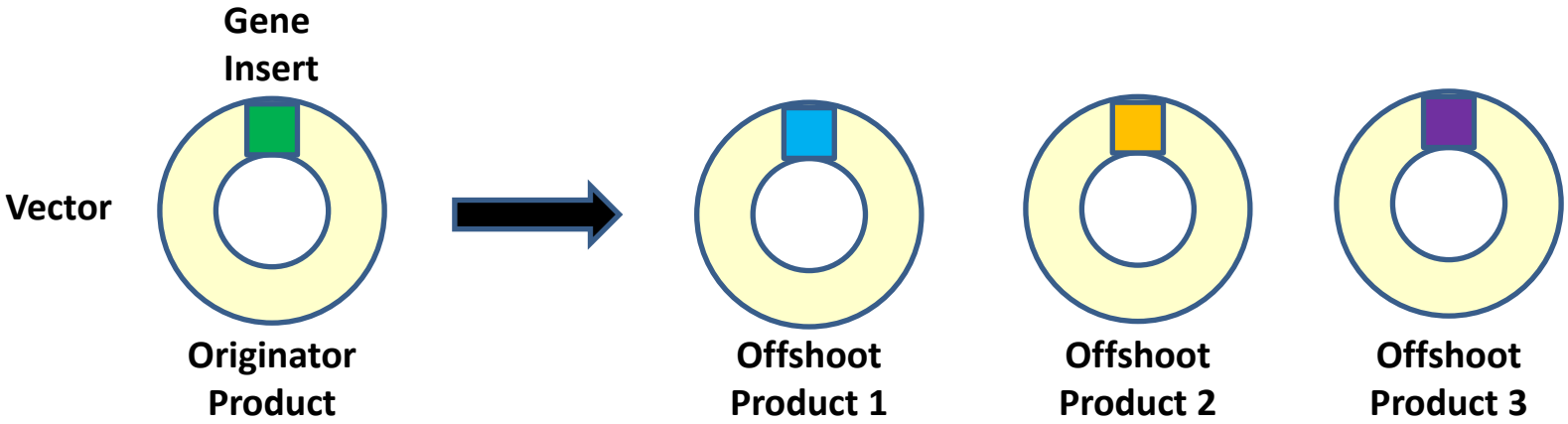
Different mode of action

Example:
Gene therapies for two different hemoglobin mutations using same vector back bone

Challenges of Individualized Therapies

- Manufacturing
- Nonclinical development
- Clinical development
- Product access

Bespoke Therapies



Premise

- In appropriate situations, non-clinical data and manufacturing information from one product may be able to be leveraged to another

Manufacturing

Current manufacturing platforms limit gene therapy production

Leveraging validated processes can potentially facilitate the development of new products

Approximate Treatment Population Per Year	1-100	>100-10,000	>10,000

Manufacturing

Will the gene therapy manufacturing platform of the future be a device?

Concepts in Development

- “Cookbook” for the development and manufacturing of bespoke therapeutics
- Leveraging of nonclinical and manufacturing data from one application to another
  - Concept of originator and offshoot products leveraging information on file and focusing on distinguishing attributes of offshoot products

Cell and Gene Therapy Challenges

- Consistency and quality of manufacturing
  - Definition of critical quality attributes
  - Potency assays
- Demonstration of clinical benefit
  - Documentation of natural history
  - Adequate size treatment benefit

CATT Meetings

CBER Advanced Technology Team

- Provides an interactive mechanism for discussion of advanced technologies or platforms needed for the development of CBER-regulated biologics products
- CATT allows access to early and ongoing interactions with CBER before filing of a regulatory submission

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt

INTERACT Program

INitial Targeted Engagement for Regulatory Advice on CBER producTs

- To further encourage early interaction with sponsors and replace the pre-pre-IND meeting process across the Center regarding preclinical, manufacturing and, clinical development plans

https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm

Summary

- FDA is committed to advancing the development of cell and gene therapies for populations of all sizes
  - Helping to individualize product development
  - Working to overcome limitations in manufacturing
  - Providing input and collaboration on novel endpoints
  - Encouraging innovative clinical trial designs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