U.S. FOOD & DRUG ADMINISTRATION

Breaking Through the Barriers to Cell and Gene Therapies

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ARM Cell & Gene State of the Industry Briefing

January 8, 2024

Overview

- Update on CAR T cell therapeutics
- Rare disease therapeutics
- State of the field of rare disease gene therapy
- How FDA plans to help address challenges

U.S. Approved Gene Therapies

- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiladrin (2022)
- Vyjuvek (2023)
- Elevidys (2023)
- Roctavian (2023)
- Casgevy (2023)
- Lyfgenia (2023)

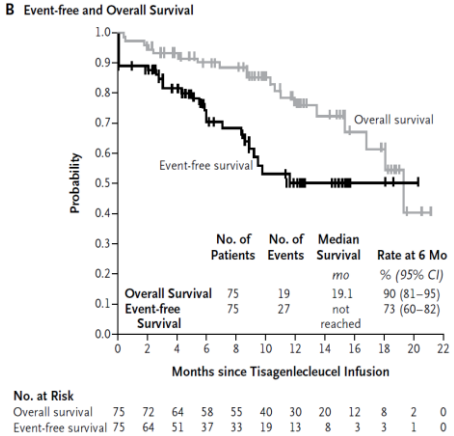
Stem cell T cell Directly administered

CAR-T Cell Update

Examples of CAR-T Cell Results

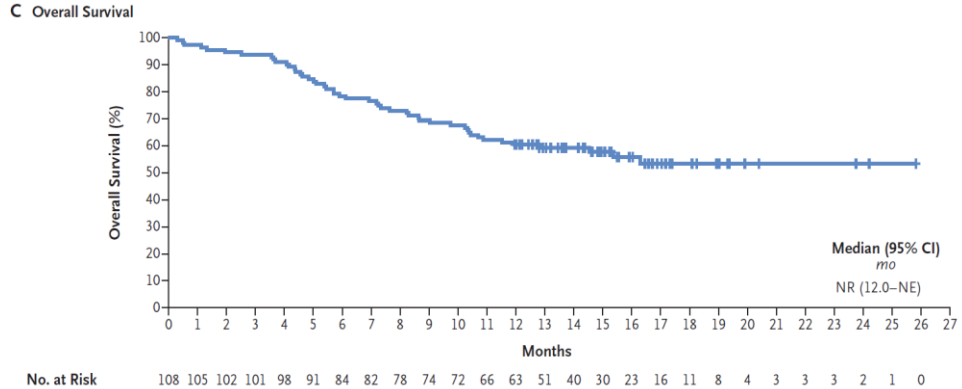
Tisagenlecleucel (Kymriah) in relapsed refractory pediatric and young adult acute lymphoid leukemia

Remission rate at 3 months of 81%



Maude SL, Laetsch TW, Buechner J et al. NEJM. 2018;378:439-448

Axicabtagene Ciloleucel (Yescarta) in relapsed refractory adult non-Hodgkin lymphoma



Neelapu SS, Locke FL, Bartlett NL et al. NEJM. 2017;377:2531-2544

Safety Concerns for CAR-T Cells

- Cytokine release syndrome (CRS) - common
- Cell-mediated encephalopathy syndrome/ immune effector cell associated neurotoxicity syndrome (CRES, ICANS)
- Others: low blood counts, transient heart dysfunction, low immunoglobulin levels
- Long-term follow up necessary to fully define

Safety Concerns for CAR-T Cells

- T Cell Malignancies (Safety alert on 28 Nov 2023)
  - T cell lymphoma, large granular lymphocytosis, others
  - 22 cases reported as of December 31, 2023, with over 27,000 individuals treated in the United States
  - Investigation ongoing: sequencing not available for all
    - Onset within 2 years reported to date (when date known)
    - Presence of CAR construct documented in a few cases

Addressing T Cell Malignancies

- Patients and clinical trial participants should be monitored life-long for new malignancies
- If a new malignancy occurs following treatment, contact the manufacturer to report the event and obtain instructions to test for the presence of the CAR transgene
- **The overall benefits of these products continue to outweigh their potential risks for all approved uses**

Gene Therapy for Rare Diseases

Importance of Therapies for Disorders that are Rare

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

Potential Rare Disease Therapeutics

- Small molecules
- Protein therapeutics
- Antisense oligonucleotides
- Gene therapy

Gene Therapy

Advantages

- Generally, administration of only one dose is required
- High possibility of success based on design
- Many different diseases can be addressed
- Long-term disease benefit or even cure possible

Disadvantages

- Complexity and cost of manufacture
- Potential for irreversible side effects
- Special expertise required for administration
- Presents challenges of a new business model

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

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

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

Current Challenges

- Gene therapy is currently at a critical juncture due to a combination of factors
  - Manufacturing challenges
  - Clinical development timelines
  - Different global regulatory requirements

Actions at Center for Biologics

- Advancing manufacturing technologies for cell and gene therapy through research
- Application of platform technology provision
- Work to more clearly define the use of accelerated approval for gene therapy
- Exploring concurrent submission and product review with other regulatory authorities
- Communication pilot for rare diseases

Manufacturing

Current manufacturing platforms limit gene therapy production

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

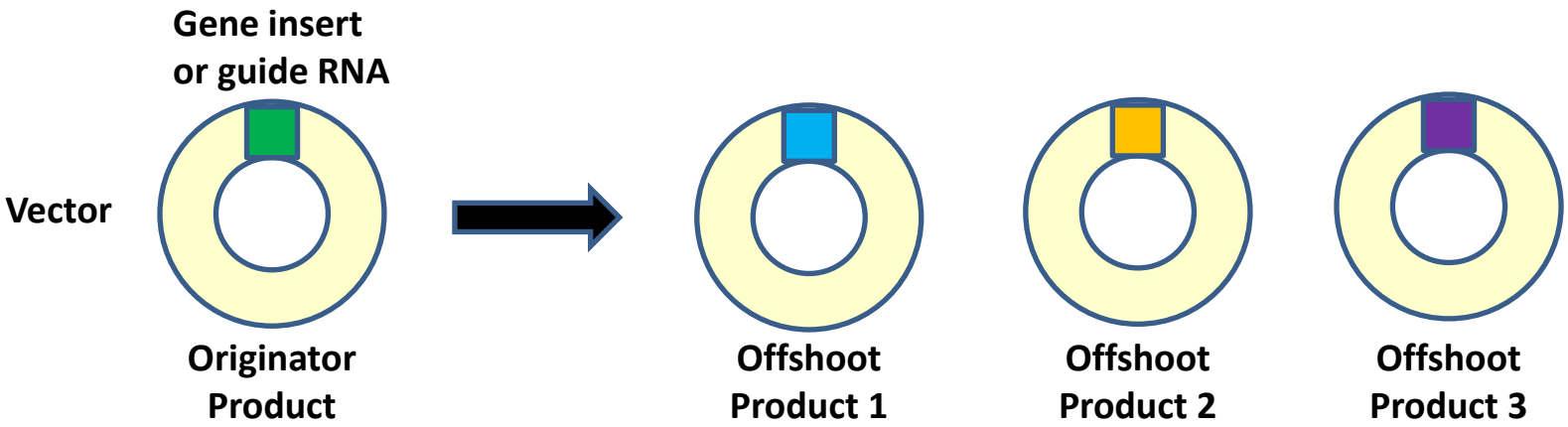
Manufacturing Solutions

- Harmonization of manufacturing protocols
  - Standardized protocol use by academics and small companies would more easily facilitate transfer of process to contract manufacturing organizations
- Automation of manufacturing process
  - Development of automated or semi-automated fabrication devices for gene therapies based on a manufacturing machine-disposable paradigm

Possible Future of Manufacturing

The small batch gene therapy manufacturing platform of the future may be a vector fabrication device that uses consumables and disposables

Platform Technologies



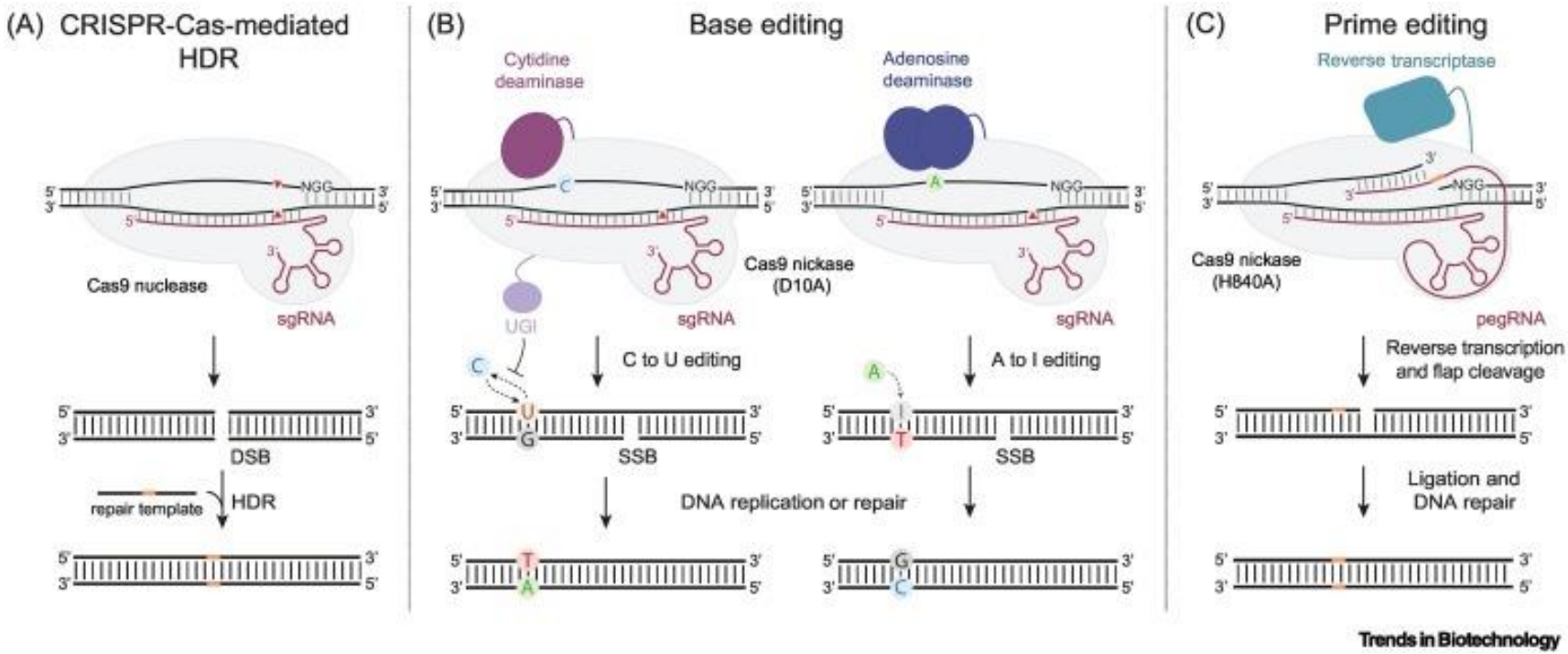
Premise

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

Omnibus Appropriations Act of 2023

- Section 2503. Platform Technologies
  - Sponsors may also “reference or rely upon data and information” from a previous application for a drug or biological product that incorporates or uses the same platform technology
  - Data must be submitted by the same sponsor or the sponsor relying on the data received permission from the sponsor who originally submitted the data
  - FDA will issue guidance relating to the program

CRISPR: Poster Child of a Platform



From: Zhou et al. Trends in Biotechnology. 2023; 41:1000-1012

Leveraging Accelerated Approval

- The science inherent in the development of many gene therapies potentially facilitates the use of biomarkers as endpoints that are *reasonably likely* to predict clinical outcomes
  - Enzyme activity levels, structural protein levels can be measured and correlated with clinical endpoints in model systems or even in humans

Connecting Biomarkers with Gene Therapy Clinical Outcomes

Animal Models

- Disease model reflects aspects of human pathology
- Administration of therapy associated with achievement of a specific protein level ameliorates disease

Human Observations

- Disease state is associated with protein levels above or below a certain range
- Certain protein levels are associated with disease absence or minimal disease

Demonstrate that equivalent protein levels can be achieved in humans affected by the disease

Collaboration on **Gen**e **T**herapies Global (CoGenT Global) Pilot

- Initial participation by Standing Regulatory Members of ICH
- Partners may participate in internal regulatory meetings and meetings that include the sponsor
- Specific regulatory reviews are shared and discussed with partners
- All meetings conducted and information shared under strict confidentiality agreements
- Goal is to increase the efficiency of the regulatory process, reducing time and cost for agencies and sponsors

Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot

- Further accelerate pace of development for products intended to address unmet medical needs in rare diseases or conditions likely to lead to significant disability or death
- Three CBER eligible products in the initial iteration to receive enhanced communications when selected for the pilot
  - An initial meeting to review features of the pilot program
  - Additional ad hoc email or live interactions on an as needed bases
  - Applications for requests to participate accepted through March 1, 2024

https://www.federalregister.gov/documents/2023/10/02/2023-21235/support-for-clinical-trials-advancing-rare-disease-therapeutics-pilot-program-program-announcement

Summary

- The Center for Biologics Evaluation and Research aims to make 2024 a breakout year addressing key challenges to the development of cell and gene therapies, especially for rare disorders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