U.S. FOOD & DRUG ADMINISTRATION

Emerging Technologies and Innovation in Manufacturing Regenerative Medicine Therapies

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NASEM Workshop

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Agenda

- Touch upon where cellular therapy is headed
- Outline key regulatory considerations
- Discuss FDA's programs facilitating product development

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)

Stem cell T cell Directly administered

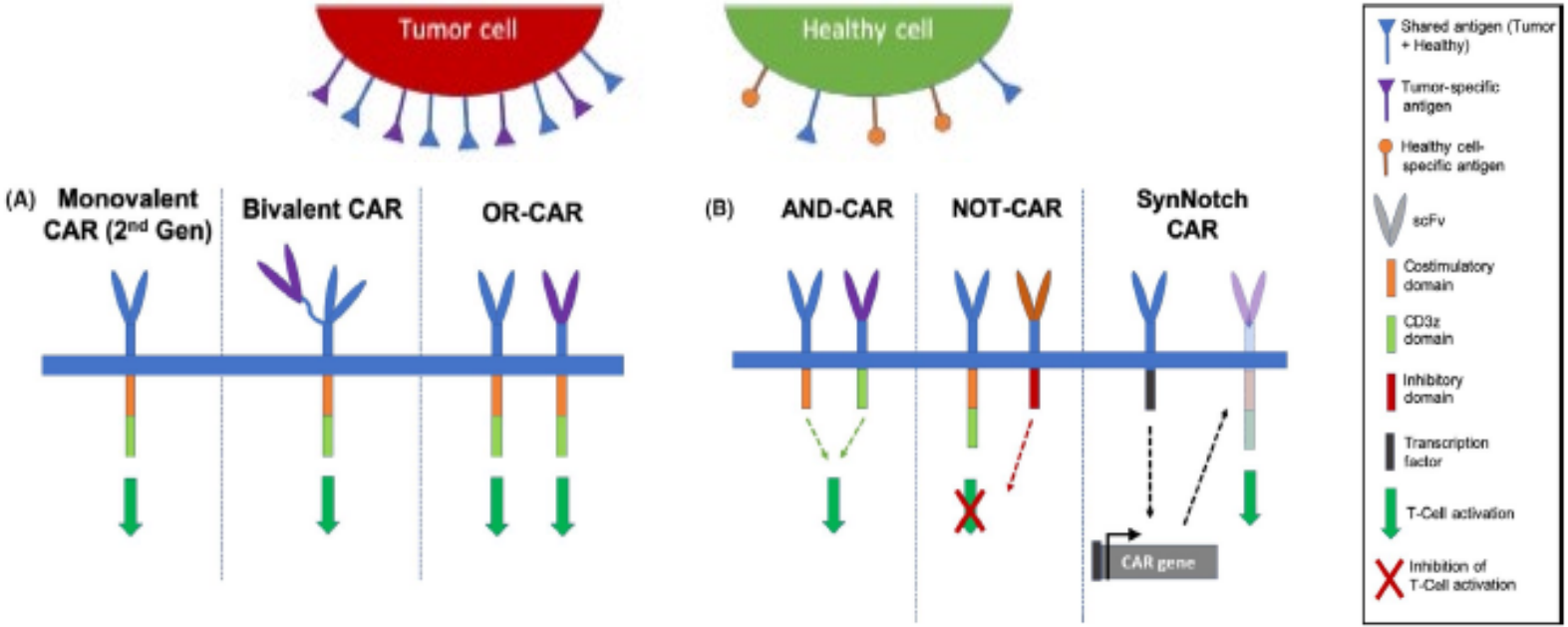
Allogeneic CAR-T Cells

- 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

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

Novel CAR-T Cell Constructs



Broadening Antigen Targeting

Narrowing Antigen Targeting

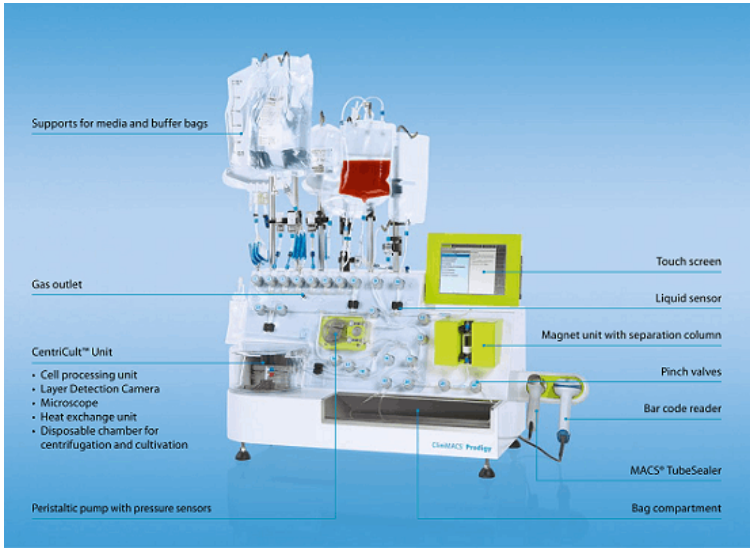
Adapted from: Walsh Z, Yang Y, Kohler ME. Immunological Reviews 2019;290:100-113

Manufacturing Considerations

- Stage appropriate chemistry, manufacturing, controls

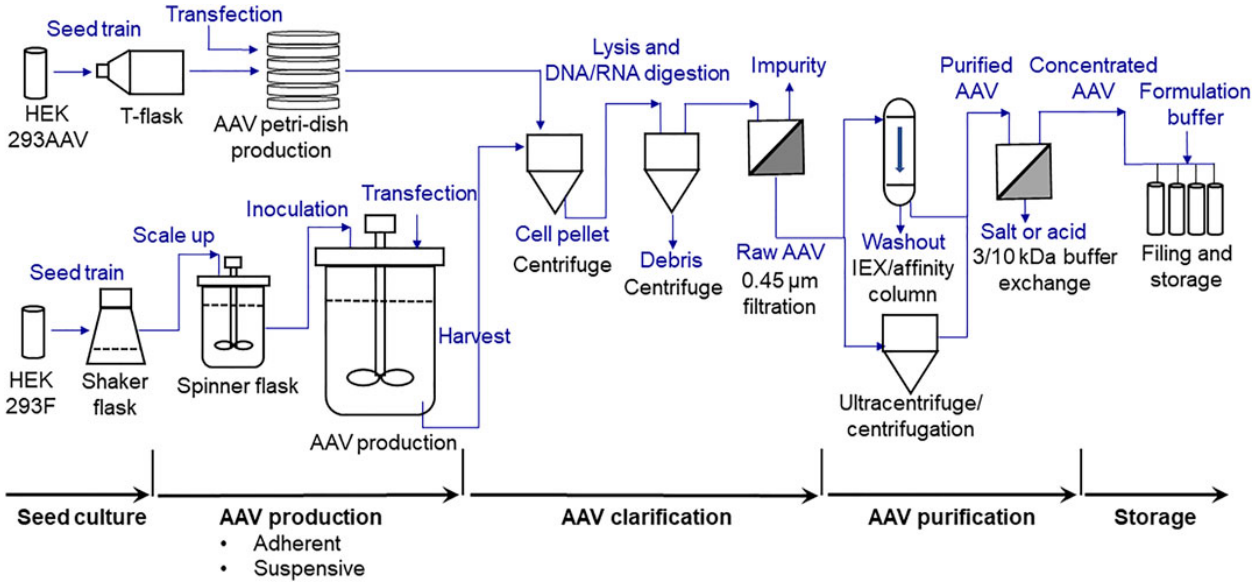
- Reagent sourcing
- Product characterization
- Potency assays
- Comparability determination

Automation of Manufacturing



Manufacturing systems for cellular therapy products

Automating Vector Production



Guan G-S et al. Process Improvement of Adeno-Associated Virus Production. Chem. Eng., 28 January 2022 Sec. Biochemical Engineering
https://doi.org/10.3389/fceng.2022.83042

Future of Vector Manufacturing?

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

July 2023 Guidance

Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products

- Considerations for management of manufacturing changes
- Regulatory reporting of manufacturing changes
- Comparability assessment and report
- Special considerations for tissue-engineered medical products

Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products | FDA

Other Relevant Recent Guidance

- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Therapies; Draft Guidance for Industry
- Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry

Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products | FDA

Human Gene Therapy Products Incorporating Human Genome Editing | FDA

Draft CAR-T Cell Guidance

- General design and development considerations
- CMC recommendations
- Preclinical recommendations
- Clinical recommendations

Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products | FDA

Draft Genome Editing Guidance

- Considerations for product development
  - General recommendations
  - Manufacturing considerations
- Considerations for preclinical studies
- Considerations for clinical studies

Human Gene Therapy Products Incorporating Human Genome Editing | FDA

Regenerative Medicine Advanced Therapy Designation (RMAT)

- Products must be intended for serious or life-threatening diseases or conditions
- Preliminary clinical evidence must indicate potential to address unmet medical needs
- Designated products are eligible as appropriate for priority review and accelerated approval

RMAT Accelerated Approval Provisions

Post-approval requirements can be fulfilled as appropriate through submission of:

- Clinical evidence, clinical studies, patient registries or other sources of real-world evidence such as electronic health records
- Collection of larger confirmatory datasets as agreed upon
- Post-approval monitoring of all patients treated with such therapy prior to approval of the therapy

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

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

Summary

- FDA is committed to working with the community interested in advancing manufacturing technologies for regenerative medicine therapies and will engage with sponsors throughout the development lifecycle from concept through postmarket surveillance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