CMC Considerations for Manufacturing of CAR T-Cell Product

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Session: New Modalities for Cancer Moonshot: Unique Regulatory, CMC and Safety Requirements for Oncology Drug Development
Chimeric Antigen Receptor T-Cells

- CARs are engineered molecules that, when present at the surface of T-cells, enable them to recognize specific proteins or antigens that are present on the surface of other cells.
- Upon cell-to-cell contact between effector and targeted cells, antigen recognition will activate the effectors and lead ultimately to the killing of cancer cells.

**CAR transduced T cells = CARTs**

- T cells transduced with construct expressing:
  - scFv against tumor antigen
  - CD3ζ signaling domain (1st gen)
  - plus costimulation domain (2nd gen)
  - Adding costimulation signal increased proliferation, t$_{1/2}$ and in vivo activity
- Suicide switch
- T-Cell Receptor (TCR) knock out
Chimeric Antigen Receptor T-Cell Therapy

**Autologous CAR Therapy (self)**
- Patient cells
- Irradiated or lymphodepleted to enhance engraftment
- Avoids GvHD (Graft vs Host disease)

**Allogeneic CAR Therapy (donor)**
- Healthy donor
- TCR knockout
- Lymphodepleted recipients
- Donor T cells can create GvHD – Donor cell TCR recognizes host MHC as foreign
  - TCR knockout technology is required
  - Cells from one donor could be used to treat many patients

Manufacture of genetically modified T cells whether derived from an autologous or allogeneic source, requires reproducibility, safety and efficacy of the final product.
Allogeneic CAR T-Cell Process

- 21 CFR 1271 EU Tissue & Cell Directives
- Frozen PBMC Multiple leukopheresis packs
- Healthy Donor

1. Activation of T-Cells
2. CAR Transduction
3. Genome Editing
5. Fill, Finish and Freeze
6. Storage
7. Shipping to clinical sites
8. Patient Dosing

- TALEN/CRISPR/Cas9
- Lentiviral and retroviral vectors
- Lentiviral and retroviral vectors
Raw Materials

• Influence of Raw materials on the final product quality
  • Identification of quality attributes and impact on product quality

• Donor starting material
  • Inherent variability
  • Donor criteria and how predicts CAR transduction, product performance

• Complex material supply chain
  • Single sources for some raw materials
  • Lack of GMP availability for some sources

• Animal and Human component materials
  • Appropriate control and testing to assure viral safety
Manufacturing Process

- Final commercial product/process in sight when designing product and manufacturing process
- Understand sources of variation and how to control
  - Reagents, donor cells, vector lots, equipment, manufacturing procedures, operators
- Understand critical steps
  - Ex. Aseptic manipulation, transduction step, conditions for cell growth, purification steps
- Understand how the manufacturing process affects purity
  - Design to remove/reduce impurities
- Determine critical quality attributes (CQA) and critical process parameters (CPP)
Comparability Considerations & Challenges

- Type of change implement
  - Scale-up, New manufacturing site, Raw material source changes
- Risk to product quality/ impact on quality attributes
- Why change is being implemented?
- Timing of change
  - Prior to pivotal vs within pivotal
- Robust analytical tool kit key
- Change can be less difficult for a well-characterized manufacturing process
- Comparability
  - Similar quality attributes before and after manufacturing change
  - No adverse impact on product quality, safety or efficacy
Product Characterization and Testing Considerations

• Safety, purity, potency
  • Incremental approach to specifications
  • Qualified potency assay required for pivotal

• Comprehensive testing panel allows for generation of data to enable process and product understanding
  • Integration and off target cleavage
  • Genetically modified cellular final product will not be completely pure
  • T-Cell subpopulations in product and effect on efficacy

• Collecting data and samples for future comparability and method bridging
Stability Considerations

ICH Q5C Stability Testing of Biotechnological/Biological Products