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Innovative Development of Closed CAR-T Platform

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Introduction

- The development of innovative advanced therapies represents a great opportunity to dramatically improve patients' lives. However, the rapid and efficient production of these advanced therapies remains a considerable challenge.
- Discuss our recent technological advancements in the process development of CAR-T cell therapy manufacturing.
- A modular approach was used to optimize unit operations to build a end to end Integrated Closed CAR-T platform process including analytical support to meet a range of therapeutic cell numbers.

CAR T-cell Platform

Process

- To support the range of doses, two closed system expansion strategies have been developed using CAR T-cells based on cell number
- The platform includes pre-evaluated and qualified equipment, technologies, and materials with developed closed unit operations.
- To enable swift onboarding of the customer process through manufacturing, WuXi has established template batch records, bill of materials, standardized testing catalog, and specifications for cGMP materials.

Low to Medium Dose	• Target <10E9 Total viable cells • One-step Expansion Strategy
High Dose	• Target >10E9 Total viable cells • Two-step Expansion Strategy

CD4+/CD8+ Isolation → Activation/Seed → Transduction → Media Addition → Expansion: →

Off-the-shelf GMP grade chemically defined media, activator, and cytokines

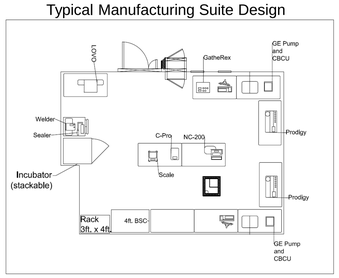
EXPANSION

Low/Medium Dose <10E9 TVC: Expansion → Harvest: Concentration/Wash Formulation/Fill

High Dose >10E9 TVC: Expansion Step 1 → Expansion Step 2 → Harvest: Concentration/Wash Formulation/Fill

Shared Manufacturing Suite

Typical Manufacturing Suite Design



- A shared manufacturing suite model has been developed to promote rapid and cost efficient manufacturing of early stage CAR T cell therapies.
- Suite equipment is certified, calibrated, monitored, maintained and IOQ completed.
- Process flows and segregation are optimized for smooth processing of multiple programs and supported by robust manufacturing coordination.
- Virtual tour of suite available.

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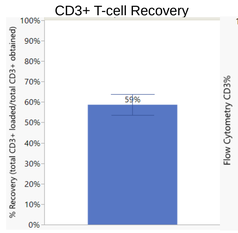
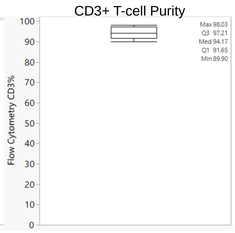
Isolation of CD4+/CD8+ T-cells

Isolation of T-cells via magnetic selection of CD4+/CD8+ T-cells by the CliniMACs Prodigy yields a ~60% CD3+ T-cell recovery with a 89-98% pure CD3+ population

CD3+ T-cell Recovery

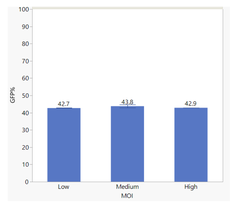


CD3+ T-cell Purity



Transduction Model

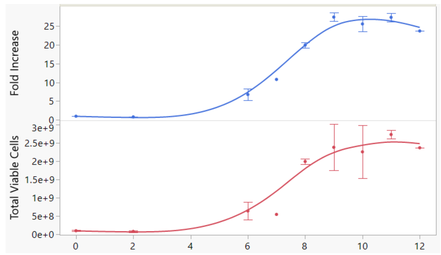
- Lentivirus transduction timing was optimized using a CAR-GFP lentivector
- Showed sufficient transduction efficiency (day7) with low MOI in scaled down model for transduction in G-Rex
- However, highly dependent on vector, GOI, and patient cells
- Target range 2-50% CAR+ cells.



One-Step Expansion Low/Medium Dose

Expansion of T-cells in G-Rex 100MCS Flasks yields 2-3E9 Total Viable Cells per Flask in 9 days

- Plateau observed around Day 9
- Yield is donor dependent
- %Viability >85%

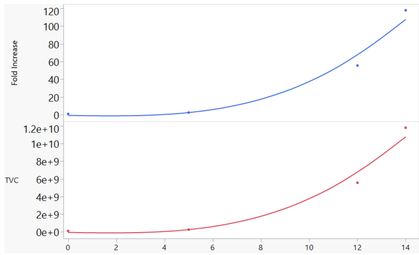


Platform can support up to (5) G-Rex 100MCS in culture yielding ~10E9 cells

Two-Step Expansion High Dose

Expansion of T-cells in G-Rex 100MCS→500MCS Flasks yields ~6E9 Total Viable Cells per Flask in 12 days

- %Viability >90%
- Donor Dependent

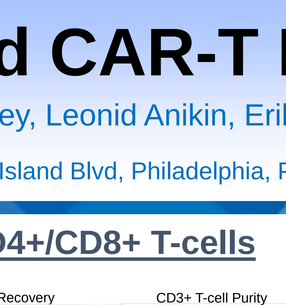


Platform can support up to (5) G-Rex 100MCS→500MCS sets in culture

Concentration/Wash, Final Formulation, and Fill

Concentration, wash, and suspension in pre-formulation buffer of the final product is completed using a closed system method.

- % Recovery following concentration and wash: > 70%
- %Viability following concentration and wash: >70%
- A variety of starting materials conditions were tested to ensure ensure high quality of wash recovery and viability
  - Starting volumes: 100-1200mL
  - Starting Cell densities: 2E6 – 1E8 cells/mL



Final product is formulated in a tested formulation buffer that is then mixed with DMSO containing cryomedia for cryopreservation in pre-evaluated cryobags.

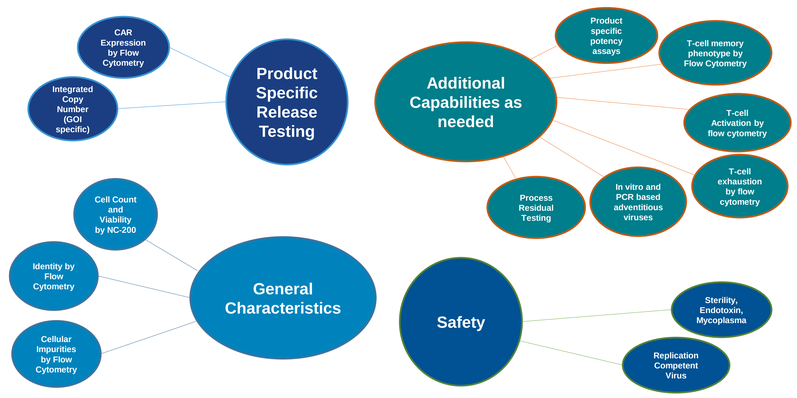
- Post-thaw evaluation of formulated cells yielded:
  - >70% recovery of cells
  - >70% viability

Final Product Characteristics

Final product characteristics are highly product and patient specific. However, final product from the platform development has yielded,

- 40-60% Naïve and central memory T-cells in the final product
- CD4+:CD8+ Ratio of 0.31-2.6

Analytical Development and Operations



- In-house testing
- Product Stability Program available in-house
- WuXi supports WuXi Manufacturing Clients, Testing Clients, and most major CMOs

Summary

- The WuXi Advanced Therapies Closed CART Platform has been designed for rapid onboarding of the customer program for GMP clinical manufacturing with a Platform process and Shared MFG suite
- Closed CART Platform Process:
  - To support the range of doses, two expansion strategies have been developed using CAR T-cells: one-step for <10 billion total viable cells, and two-step for >10billion total viable cells. Both strategies yield high viability cells (>85%)
  - Closed Concentration/wash, final formulation, and fill platform parameters have yielded >70% Recovery and viability.
  - Time efficient due to prepared Bill of materials, template batch records, trained operators, and qualified shared manufacturing suite
- An analytical platform has been developed to production of CAR T-cell therapy, which allows for efficient release testing.
- Experienced regulatory support available for Type A,B,C FDA meetings, IND, BLA, DMF authoring and submission as well as CMC, Facility and Material controls, providing end-to-end services