Transitioning to Scalable Bioreactors for Allogeneic iPSC-Derived Cell Therapies: Cost Savings and Global Patient Access

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832

ABSTRACT:

Allogeneic iPSC-derived cell therapies provide an "off-the-shelf" alternative to autologous CAR-T approaches, aiming to reduce costs and enabling greater patient access through scalable production, automation, and streamlined quality control. CNTY-101, an allogeneic iPSC-derived NK cell product with a CD19-targeting CAR and gene edits to enhance persistence, safety, and immune evasion, exemplifies these advantages. With the ability to generate large quantities of therapeutic cells from a clonal iPSC master cell bank, iPSC therapies bypass logistical complexities of patient-specific processes, offering scalable solutions for clinical and commercial use.

To meet clinical demand for high-dose and repeat administration (e.g., up to 9 billion cells per dosing cycle), a robust multi-stage manufacturing process has been developed, producing >6×10^{10} fully differentiated NK cells per batch. Transitioning from static cell cultures to scalable suspension bioreactors has enabled significant yield improvements and cost reductions. Critical process parameters such as inoculation density, agitation, gassing strategy, and perfusion rates were optimized, leading to an >8-fold increase in cell yield while maintaining product quality (>90% viability, >98-99% purity).

The implementation of rocking and stirred-tank bioreactors, in conjunction with optimized perfusion and feeding strategies, achieved cost reductions of 50-70% in raw materials and consumables. Enhanced automation and real-time monitoring improved process controls, operational efficiency, and scalability. These advances position scalable biomanufacturing as a cornerstone for global accessibility to allogeneic iPSC-derived therapies, with clinical study (CALiPSO-1/NCT06255028) further supporting this potential.

Building A Next Generation Allogeneic Cell Therapy Platform

iPSC Reprogramming

- Comprehensive collection of clinical grade lines (CD34+ HSC, αβ T cell, γδ T cell derived)
- Internal clinical line reprogramming capabilities

Gene Editing

- Proprietary gene-editing platform
  - CRISPR MAD7-derived gene editing for precise transgene integration

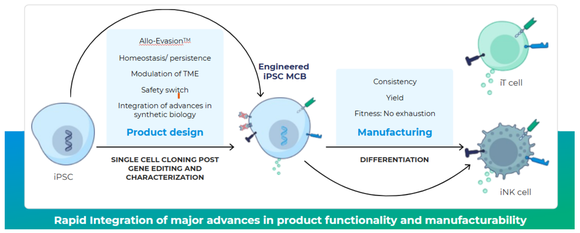
iPSC Differentiation/Manufacturing

- Scalable protocols and processes to produce highly functional iNK and iT cell products

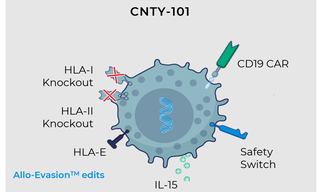
Protein Engineering

- Developing proprietary next-generation CARs
- Universal tumor targeting platform

Century's next-generation allogeneic iPSC technology platform:
Versatility and unprecedented control



CNTY-101: Differentiated Next-Gen CD19 Targeted Product



Delivering on our vision to change the cell therapy treatment paradigm

- Goal to improve tolerability and ease of outpatient administration
- Potential to eliminate need for lymphodepletion with subsequent cycles of therapy
- First CD19-targeted agent to test durability benefit of repeat dosing enabled by Allo-Evasion™ edits

CNTY-101 Approved US IND

ELiPSE-1 (NCT05336409) IND

- A Study of CNTY-101 in Participants with CD19-Positive B-Cell Malignancies

CALiPSO-1 (NCT06255028) IND

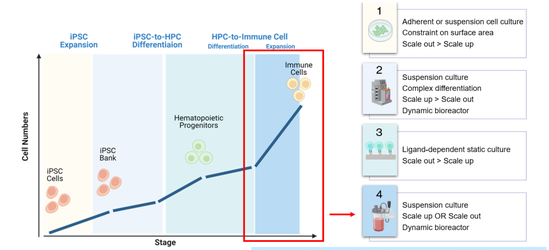
A Study of CNTY-101 in Participants With Refractory B Cell-mediated Autoimmune Diseases

CNTY-101 Clinical Updates

ASH 2023:
Multiple Doses of CNTY-101, an iPSC-Derived Allogeneic CD19 Targeting CAR-NK Product, Are Safe and Result in Tumor Microenvironment Changes Associated with Response: A Case Study. Blood Volume 142, Supplement 1, 2 November 2023, Page 1654

ASCO 2024:
Interim results from the ELiPSE-1 study: A phase 1, multicenter, open-label study of CNTY-101 in subjects with relapsed or refractory CD19-positive B-cell malignancies. J. Clin Oncol 42, 2024 (suppl 16; abstr 7023)

Important Considerations for iPSC-derived Cell Therapies



Opportunity to scale up the process with bioreactor development at late stage of the process

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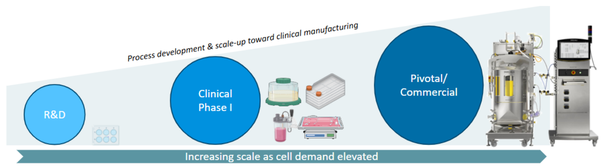
Phase-appropriate Clinical Scale Demand

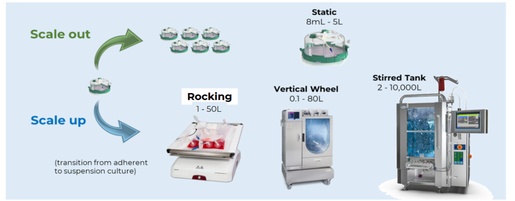


Factors dictate clinical demands
- Patient numbers
- Clinical doses

Determine strategy of process scale-up
- Culture system selection
- Process parameters identification
- Operational complexity

Development to ensure robust manufacturing
- Operation range
- Batch size and numbers
- Cost of goods

Bioreactor Options



Cost Break-Down per Batch

Yield	↑
Materials and FTE	↑
Suite Cost (Facility)	–

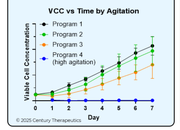
Cost Break-Down per Campaign

Number of batches required	↓
Start-Up Costs	↓
Materials and FTE	↓
Analytical testing	↓

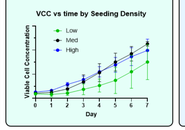
Assuming to support same patient number with same amount for vial required

Parameter Optimization on Xuri Bioreactor (iNK)
-for scaling from 2L to 10L

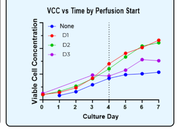
Agitation
- Determine better expansion within Program 1 and 2
- Noticeable drop in VCC and viability with Programs 3 and 4



Seeding Concentration
- Similar fold change between seeding concentration but increased final VCC in medium seeding densities.
- Reduced performance at higher seeding densities

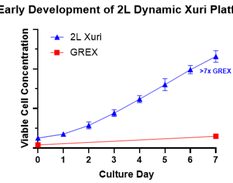


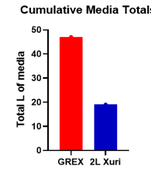
Timing of Perfusion
- D1 and D2 initiation of perfusion are comparable with reduced media usage by starting later
- Starting too late in culture impacts performance



Xuri Process Development

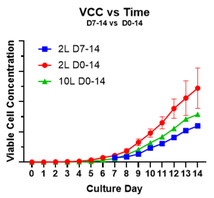
Dynamic culture provides an opportunity for increased yield and scale-up potential as opposed to scale-out

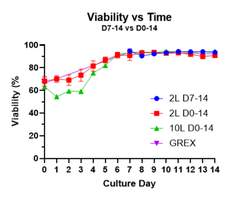




- >7x viable cell density in dynamic process over 1 week and multiple NK platform cell lines
- 40% reduction in media requirements with Xuri perfusion relative to static cultures
- Numerous opportunities for optimization
  - Agitation, Seeding density (optimized in static system), perfusion media composition and rate, DO/pH control

Transition from 2L to 10L NK Scaling Provides Path Forward

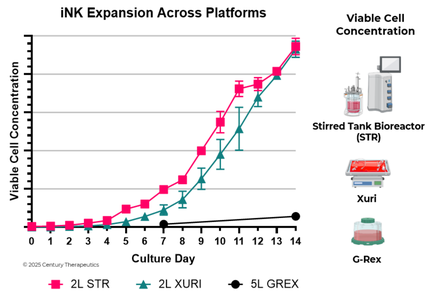




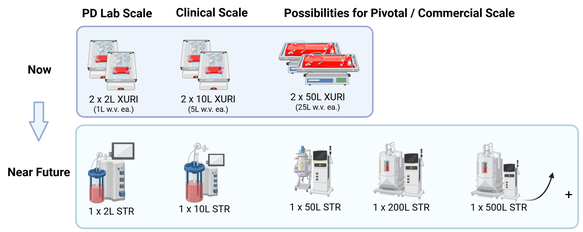
- Scaling up to 10L iNK Xuri process has yielded strong harvest densities and viabilities
  - Xuri 10L slower cell growth compared to 2L between D0-14, but improved compared to 2L D7-14
- Optimize early viability to align with 2L and GREX; enhance yield consistency

Stirred Tank Process Development

STR Early Development - Promise in Scalable, Dynamic Systems



Stage-Optimized Platforms for Clinical Applications



Depending on the indication and yield requirement, XURI is a great intermediate bioreactor to meet demands, but **the STR is scalable enough to meet any demand in the product's lifetime**.