CENTURY THERAPEUTICS

Process Scale up for the Production of iPSC-Derived Beta Islets for Type I Diabetes

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CASSS Cell and Gene Therapy Meeting
October 21, 2026

Outline

1. Century background
2. CNTY-813 and AlloEvasion™ to reduce or eliminate immunosuppression
3. Scaling up CNTY-813 for commercial manufacturing
4. Scale up principles and learnings from the biotech field

* Verhoeff et al., Transplantation, 2015, 109(1): 22–35

Century Therapeutics: Advancing Curative Medicines Through Cell Engineering

Powered by The Cell Foundry and Allo-Evasion™ 5.0

Foundational Platform Tech:
Engine to create and scale cellular medicines

The Cell Foundry: Enables scalable generation of highly functional iPSC-derived therapies

Allo-Evasion™ 5.0: Leadership in immune-evasive cell design

Integrated Know-How: Deep functional expertise internally, integrated from discovery to manufacturing and development

Targeting Functional Cures:
T1D and Autoimmune disease

CNTY-813: iPSC-derived, immune-evasive islet replacement therapy for type 1 diabetes

Islet replacement is clinically validated; CNTY-813 aims to deliver this without chronic immunosuppression, at scale

Pipeline: Foundational technology powers:

- CNTY-308, an iPSC-derived, immune-evasive αβ T cell with potential across autoimmune disease
- Next-gen discovery programs across multiple cell types and targets

Well Funded:
Multiple Anticipated Near-Term Milestones

Recent Funding

Oversubscribed $135M PIPE in early 2026 provides runway into Q1 2029

Key Anticipated Near-Term Milestones

- ❑ CNTY-813 oral presentation at EASD 2026
- ❑ CNTY-813 IND submission expected 4Q 2026
- ❑ CNTY-308 expected in clinic in 2026
- ❑ Clinical data expected 2H 2027 for CNTY-813

Focused. Funded. Executing.

© 2026

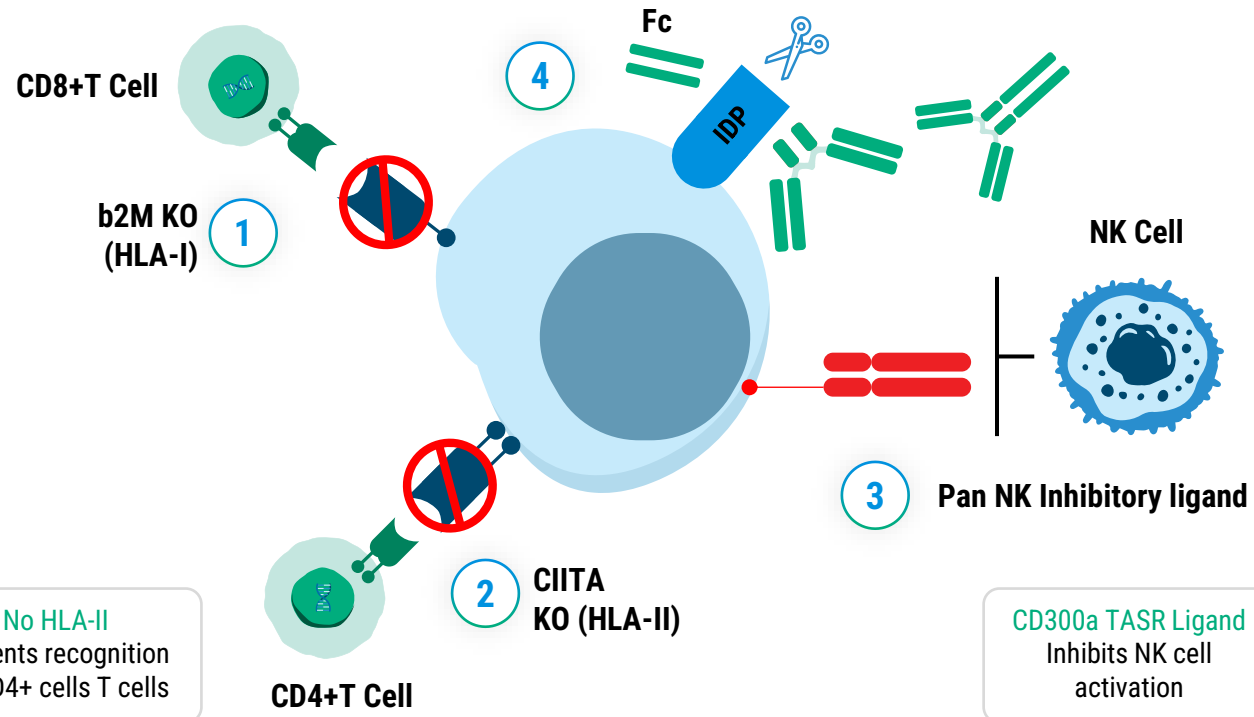
Century's potential solution to T1D is leveraging iPSCs + ALLO-EVASION™ 5.0

CNTY-813: scalable, iPSC-derived islet replacement therapy engineered to eliminate the need for immunosuppression

ALLO-EVASION™ 5.0: Evading cell-mediated and humoral responses

No HLA-I
Prevents recognition by CD8+ cells T cells

IgG Cleavage
Reduces Fc binding and humoral activity



No HLA-II
Prevents recognition by CD4+ cells T cells

CD300a TASR Ligand
Inhibits NK cell activation

Protection from:

T cells	1 Deletion of HLA-I 2 Deletion of HLA-II
NK cells	3 Insertion of CD300a TASR pan-NK inhibitory ligand[1, 2]
Humoral Immunity	4 Insertion of cell-surface enzyme to degrade IgG antibodies[3]

1. https://www.centurytx.com/wp-content/uploads/ASH_Welstead_Universal-Protection-of-Allogenic-T-Cells-Final.pdf
2. https://ashpublications.org/bloodadvances/article/doi/10.1182/bloodadvances.2024013436/518079/Universal-Protection-of-Allogeneic-T-Cell
3. Peraro et al, *Mol. Therapy* 2021, 29(12), 3398-3409; https://pmc.ncbi.nlm.nih.gov/articles/PMC8636170

In-house manufacturing at scale: A competitive advantage built from experience

Reproducible, scalable cell product from a single master cell bank to clinical supply



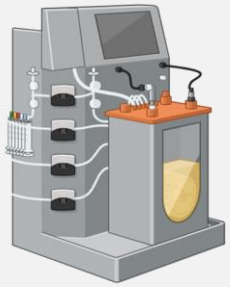
53,000 sq ft cGMP facility

- Built-for-purpose facility producing and releasing cell therapy product
- In-house team from development through clinical supply — aligned priorities, faster iteration, IP protected
- Capacity and design suited for early commercialization



Single donor master cell banks

- Clonal origin enables a well-characterized, homogeneous product
- Batch-to-batch consistency maintained over the product lifetime
- Multiple back up lines ensure redundancy and next generation product potential



Scalability with bioreactors

- Suspension-based iPSC differentiation is scalable from research to clinical manufacturing
- Batch-to-batch reproducibility demonstrated across independent runs
- Processes scalable to hundreds of liters — Broad patient access, reduced cost of goods

Source: Company data on file.

CNTY-813:

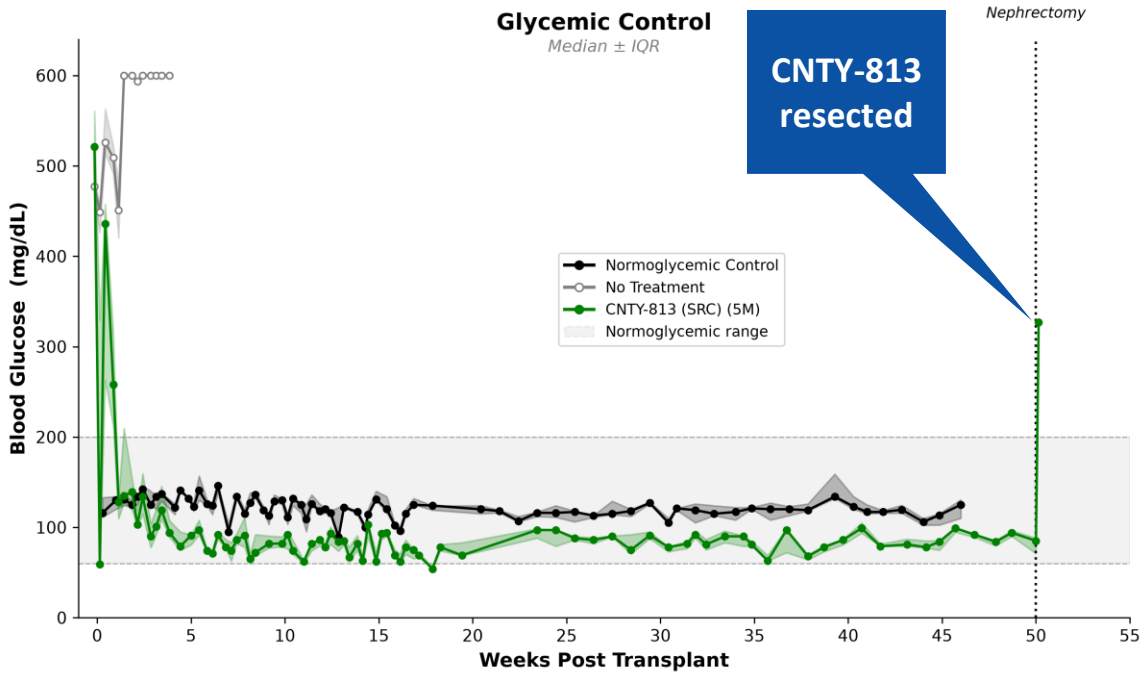
Islet function, immune-evasive engineering, and scalable manufacturing address key barriers for T1D cell replacement

- In vitro and in vivo data support potential to provide functional cure without systemic immunosuppression
- Clinical candidate selected with Century's Allo-Evasion™ 5.0 to protect cells from immune rejection and disease-related autoantibodies
- A fully scalable, bioreactor-enabled differentiation process yields mature, functional islets from engineered iPSCs for Phase 1 clinical trials and beyond

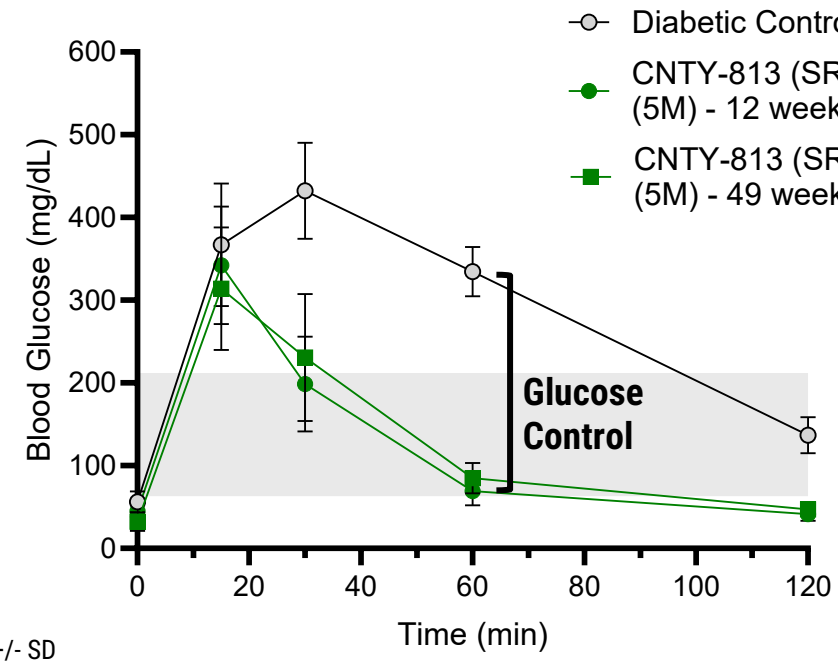
CNTY-813 islets rapidly restored normoglycemia in STZ-induced diabetic mice

Preclinical Potency

Non-Fasted Blood Glucose



Glucose Tolerance Test



Mean +/- SD

Allo-Evasion™ 5.0-edited CNTY-813 restored glucose control for >11 months

STZ = Streptozotocin | SRC = Sub renal capsule implantation, Gray shaded area = normal blood glucose range

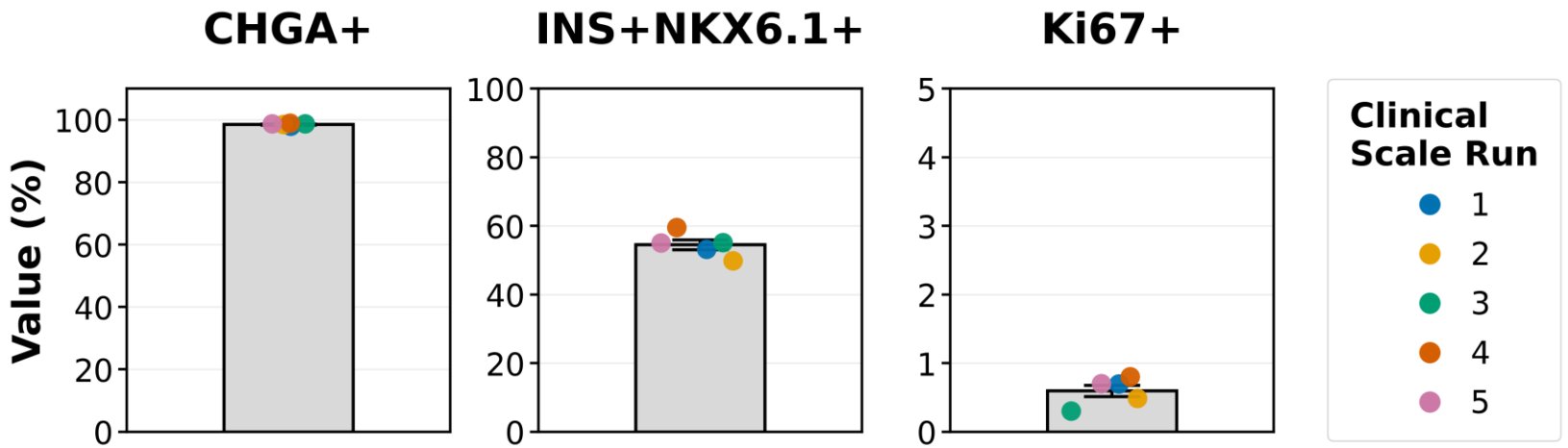
Source: Company data on file

Phase 1 clinical manufacturing process established and executed from MCB across multiple independent batches

MCB Thaw | iPSC Expansion | Bioreactor Differentiation | Cryopreserved Intermediate | Post-Thaw Maturation | Final Fresh Product



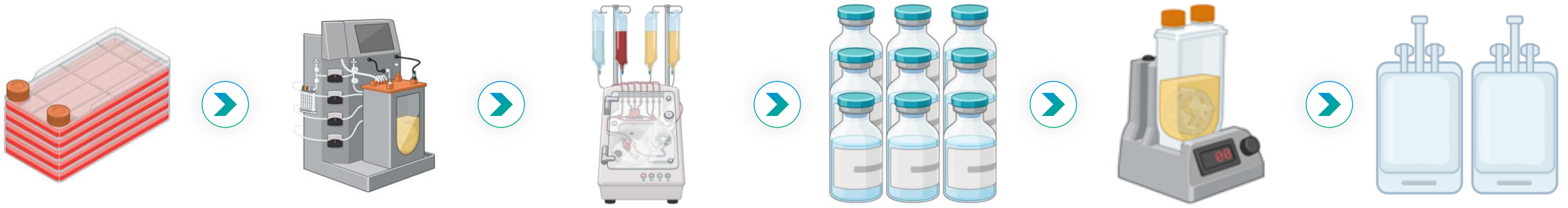
Consistent final product flow cytometry profiles across 5 clinical-scale batches



Source: Company data on file

CNTY-813 Phase 1 clinical manufacturing process

iPSC Expansion | Bioreactor Differentiation | Harvest | Cryopreserved Intermediate | Post-Thaw Maturation | Final Fresh Product

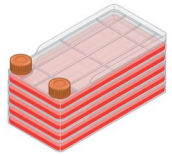
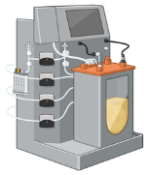
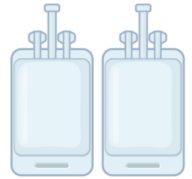
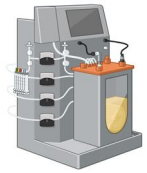
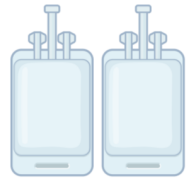


Limited doses per batch

High Cost of Goods (COGs) and labor requirements

Multiple manipulations and some open steps → increased execution risk

CNTY-813 Phase I vs. Intended commercial manufacturing process

iPSC Expansion	Bioreactor Differentiation	Harvest	Cryopreserved Intermediate	Post-Thaw Maturation	Final Fresh Product
 2D			 few patients		 1 patient
 3D	 Multiple 50–800 L		 1000's of patients	 10–50 L	 10's to 100's of patients

A fundamental scale up approach is needed for all unit operations



Cell Expansion and Differentiation (Bioreactor)



Cell Harvest (Counterflow Centrifuge or Alternating Tangential Flow Filtration)



Drug Product Filling (Automated Vial Filler)

Engineering Expertise Leveraged from Other Cell Therapies and Biologics

- Established engineering principles
- Understanding scale up parameters
- Modeling to predict scale up success
- Scale up data to refine and confirm models

Bioreactor options: Continue with PBS Vertical Wheel or switch to Stirred Tank

Vertical Wheel
0.1–80L



Stirred Tank
2–10,000L



Key Scale-Up Challenges

- O_2 supply and CO_2 removal
- Mechanical cell damage
- Maintaining aggregate size
- Mixing
- pH control

Comparison of PBS and Stirred Tank

	Largest Scale Available	Scale Up Characterization	Comparability Challenge
PBS	80 L (maybe 500 L)	Some, with work in progress	Minimal
STR	200–800 L (or greater)	Extensive	More challenging

****Leverage scale-up expertise from biologics field and previous cell therapy bioreactor technology****

Stirred Tanks up to 30,000 L have been used for production of antibodies with mammalian cells

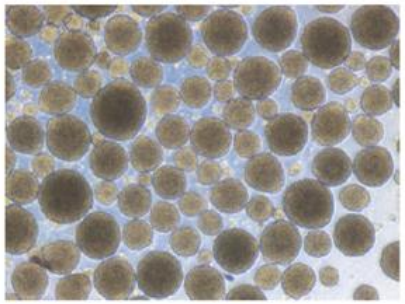
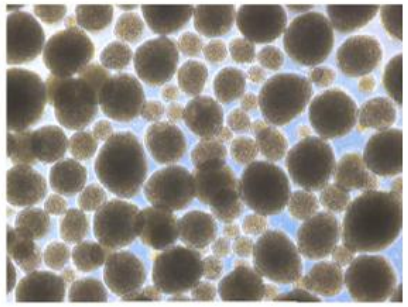
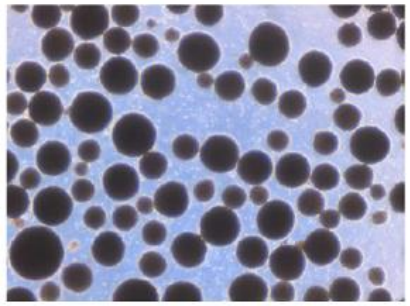
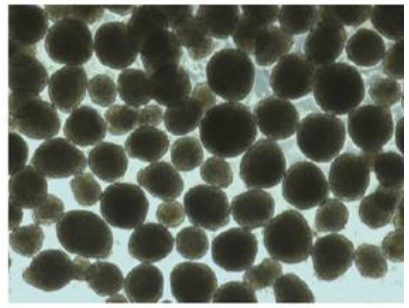
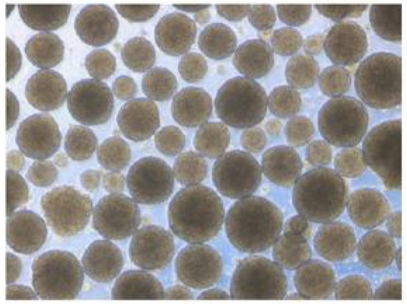
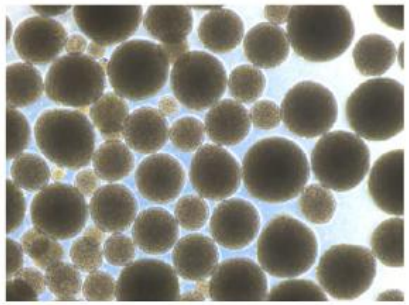
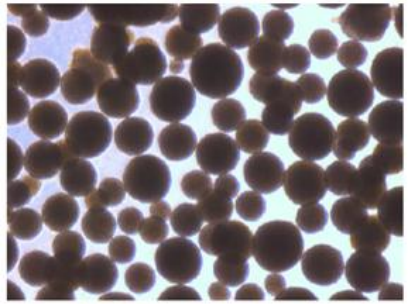
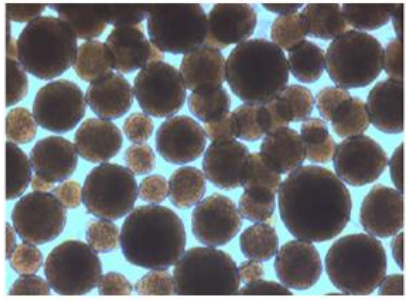
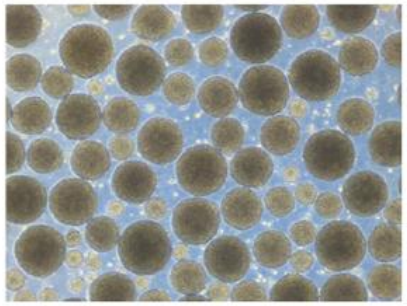
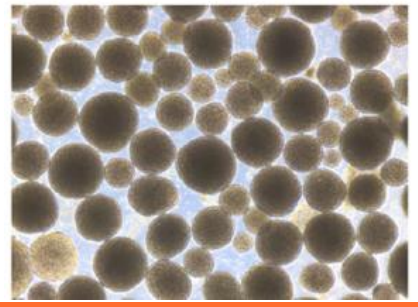
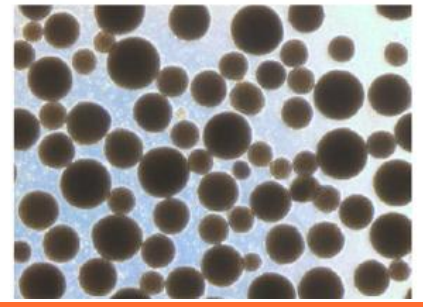
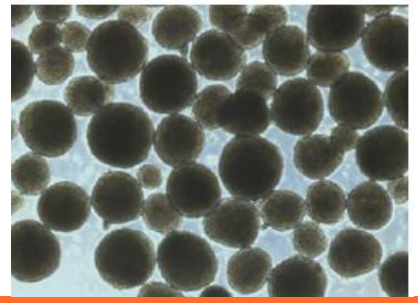


Large-scale, stainless-steel plant for MAb production from CHO cells (Genentech)

Scale Up of iPSC Differentiation to Endocrine Cells in Vertical-Wheel Bioreactors (VWB) at 3L and 80L Scales

PBS BIOTECH® ACCELERATING THERAPIES FROM START TO SCALE

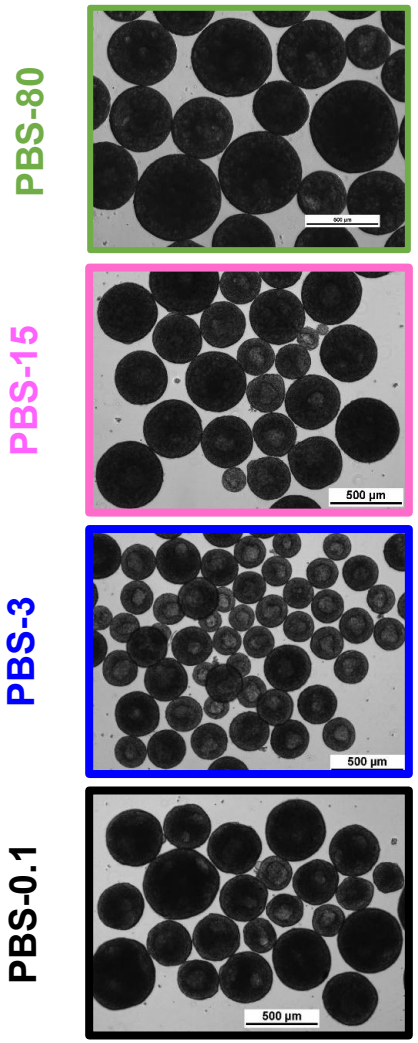
Courtesy of VIACYTE Regenerating Health™

		Stage 1 (D2)	Stage 2 (D5)	Stage 3 (D8)	Stage 4 (D12)
Roller Bottle					
PBS-3 VWB					
PBS-80 VWB					

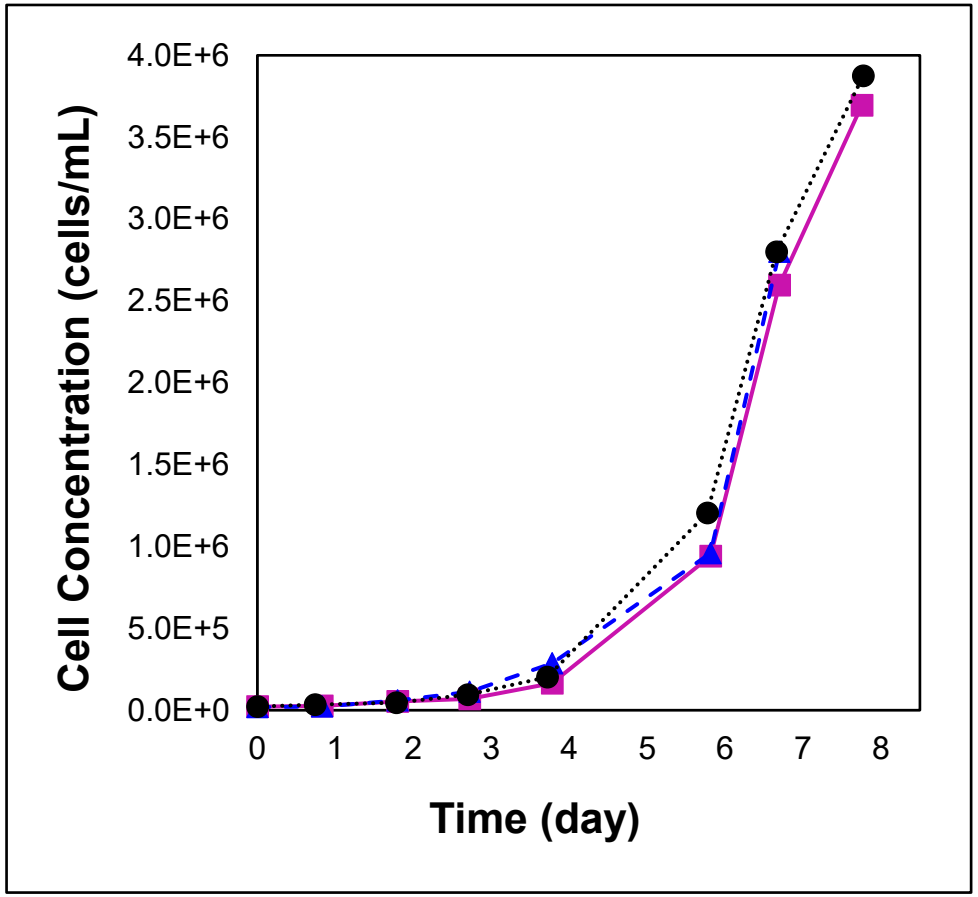
Linear Scalability of Undifferentiated iPSC Expansion in Vertical-Wheel Bioreactors (VWB) from 0.1L to 80L Scales

PBS BIOTECH® | ACCELERATING THERAPIES FROM START TO SCALE

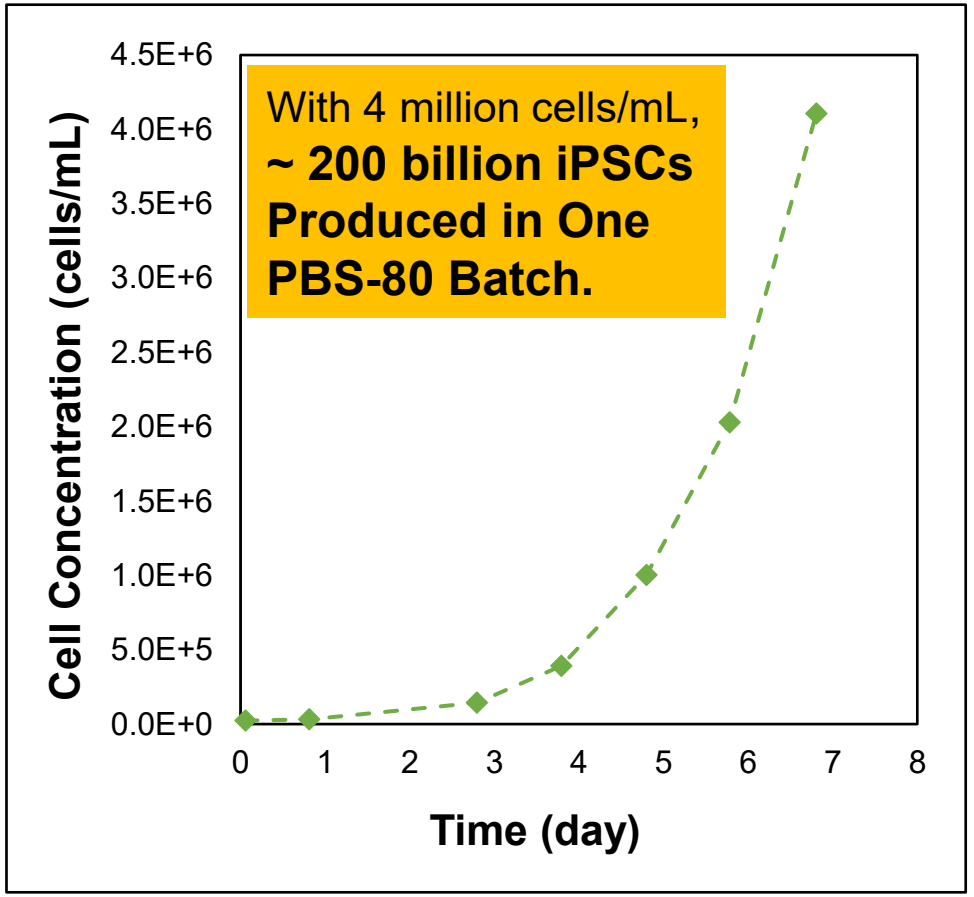
Cell Aggregates (D6)



PBS-0.1, PBS-3, and PBS-15

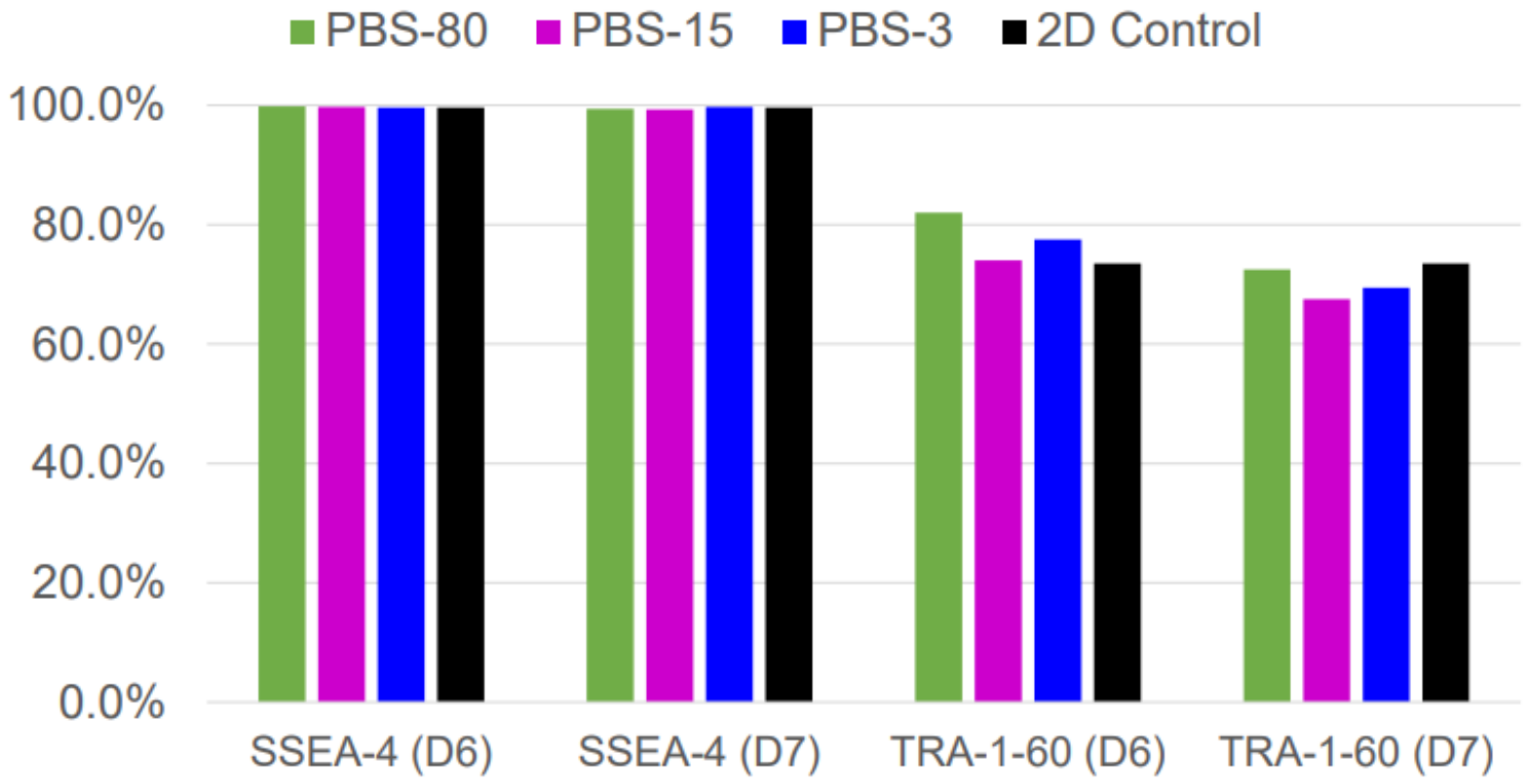


PBS-80 (50L Working Volume)



Consistency of Pluripotency Marker Expression During Manufacturing Process Scale Up

PBS BIOTECH® ACCELERATING THERAPIES FROM START TO SCALE



Cell Line: TC1133
Medium: HBM



How high can we scale a beta islet process in a Stirred Tank Bioreactor

CHO cultures for biologics scaled to 30,000L

- Single cell suspensions

Anchorage-dependent cells grown on microcarriers scaled to 1000 L

- Typical microcarrier diameter: 200 µm
- Largest published scale: 1000 L for production of polio vaccine with Vero cells (Montagnon et al., 1984, Dev Biol Stand, 55: 37–38)

What about beta islets growing as aggregates?

- Typical islet aggregate diameter is 200 µm (for example, from Shapiro lab*)
- That's similar to MCs but…
- Oxygen uptake rate will affect power per unit volume which affects turbulent flow
- Need to understand this better and model potential bioreactors to predict Kolmogorov eddy size and find conditions that result in eddies >150–200 µm throughout the bioreactor
- Why 150 µm and what are Kolmogorov Eddies?

* Verhoeff et al., Transplantation, 2015, 109(1): 22–35

Cell damage by mechanical agitation

- Possible damage mechanisms (Cherry and Papoutsakis, Biotechnol Bioeng, 1988, 32: 1001–1014)
  - Microcarrier-microcarrier or aggregate-aggregate collisions
  - Collisions with impeller or other bioreactor parts
  - Interactions with turbulent eddies
- Kolmogorov eddies with a range of sizes exist in turbulent liquid
- Smallest eddies have size (η) of:

$$\eta = \left(\frac{\upsilon^3}{\varepsilon}\right)^{1/4}$$

η = Eddy length
υ = Kinematic viscosity
ε = Rate of turbulent energy dissipation per mass of liquid

Croughan et al., Biotechnol Bioeng, 1989, 33: 862–872
Lakhotia and Papoutsakis, Biotechnol Bioeng, 1992, 39: 95–107

- If η >> cell, microcarrier, or aggregate diameter, then eddy rapidly accelerates cell, microcarrier, or aggregate
- If η is 50–67% or less of cell, MC, or aggregate diameter, cells, MC or aggregates are too large to be accelerated so eddy dissipates its kinetic energy against cells, MC, or aggregate
- Scale-up challenge: At increasing scales: Power input/volume ↑, ε↑, η ↓
- Need to operate at low rpm to achieve eddy sizes greater than aggregate diameter throughout the bioreactor
- Low rpm may result in aggregates that are too large or poor mixing

Other bioreactor scale-up considerations



Agitation

- Constant impeller tip speed OR
- Constant specific energy dissipation (power/unit volume)
- Tradeoffs: High shear can damage cells; low rpm might result in aggregates that are too large and might not give sufficient mixing



Air/O_2 flow

- Constant volumetric flow of gas per liquid volume (vvm) OR
- Constant superficial velocity (v_S)
- Tradeoffs: Low flowrate can lead to CO_2 accumulation; high flowrate can lead to foaming and clogging vent filter



General Strategy

- Operate within some acceptable agitation & air/O_2 flow windows to achieve sufficient oxygenation and CO_2 removal
- Utilize scale-down models to define acceptable windows and confirm at large scale

Scale-Up of Agitation

A. Constant Impeller Tip Speed

$$ITS = \pi N D_i$$

N: Impeller speed (t^{-1})
D_i: impeller diameter

B. Constant Power per Unit Volume

Dimensionless Power Number (N_p) is defined as:

$$N_p = \frac{P_0}{\rho N^3 D_i^5}$$

P_0: Ungassed power input
ρ : Fluid density

Power Number is constant for a given impeller type in turbulent regime (as defined by Impeller Reynolds number) and is relatively independent of geometry and position

Scale-Up of Agitation (cont'd)

B.
Constant Power per Unit Volume

Assumptions:

- Gassed impeller power is proportional to ungassed power
- Power dissipated due to aeration is consistent upon scale-up
- Multiple impellers are additive

$$N_p = \frac{P_0}{\rho N^3 D_i^5} \qquad \frac{P}{V} = \frac{N_p N_i N^3 D_i^5 \rho}{V}$$

P: Gassed power input
V: Working volume
N_i: number of impellers

Constant P/V means $P_1/V_1 = P_2/V_2$
Np and ρ are constant upon scale-up; therefore:

$$\left(\frac{N^3 D_i^5}{V}\right)_{Scale1} = \left(\frac{N^3 D_i^5}{V}\right)_{Scale2}$$

for case where N_i is constant upon scale-up

Example of 10-Fold Scale-Up

Case where $Di_2 = 2 \times Di_1$

Constant P/V:
$N_2 = 0.67\ N_1$
$ITS_2 = 1.36\ ITS_1$

Constant ITS:
$N_2 = 0.5\ N_1$
$P/V_2 = 0.41\ P/V_1$

Tradeoff:

- High shear can damage cells; low rpm might result in aggregates that are too large and might not give sufficient mixing (quantitated by t_{mix})
- Also, P/V influences k_La; must ensure proper oxygenation

Scale-Up of Air (or O_2) Flow

A.
Constant volumetric flow of gas per liquid volume (vvm)

$$vvm = \frac{Q}{V_L}$$

vvm: Gas volume flow rate per liquid volume

Q: Volumetric gas flow rate

V_L: Liquid volume

B.
Constant superficial gas velocity

$$v_s = \frac{Q}{A_c}$$

v_s: Superficial gas velocity

A_c: Tank cross-sectional area

Tradeoff:

- Constant vvm means v_s increases with scale-up and could lead to foaming
- Constant v_s means vvm decreases with scale-up and could lead to CO_2 accumulation

Example of 10-Fold Scale-Up

Case where $D_{T2} = 2 \times D_{T1}$ (D_T: Tank Diameter)

If we scale airflow on constant VVM:

$$\text{vvm} = \frac{Q}{V} \qquad v_s = \frac{Q}{A_c} \qquad \textbf{So: } vvm = \frac{v_s A_c}{V}$$

$$\text{vvm}_1 = \text{vvm}_2 \qquad \left(\frac{v_s A_c}{V}\right)_1 = \left(\frac{v_s A_c}{V}\right)_2$$

$$\nu_{s,2} = \left(\frac{V_2}{V_1}\right)\left(\frac{D_{T,1}}{D_{T,2}}\right)^2 \nu_{s,1} \qquad V_2 = 10\ V_1 \rightarrow \qquad \nu_{s,2} = 2.5\ \nu_{s,1}$$

If we scale airflow on constant Vs:

$$v_s = \frac{Q}{A_c} = \frac{vvm \cdot V}{A_c} \qquad \left(\frac{vvm \cdot V}{A_c}\right)_1 = \left(\frac{vvm \cdot V}{A_c}\right)_2$$

$$\text{vvm}_2 = \left(\frac{V_1}{V_2}\right)\left(\frac{D_{T,2}}{D_{T,1}}\right)^2 vvm_1 \qquad V_2 = 10\ V_1 \rightarrow \qquad \text{vvm}_2 = 0.4\ \text{vvm}_1$$

Principles of separation in continuous centrifugation for harvesting cells

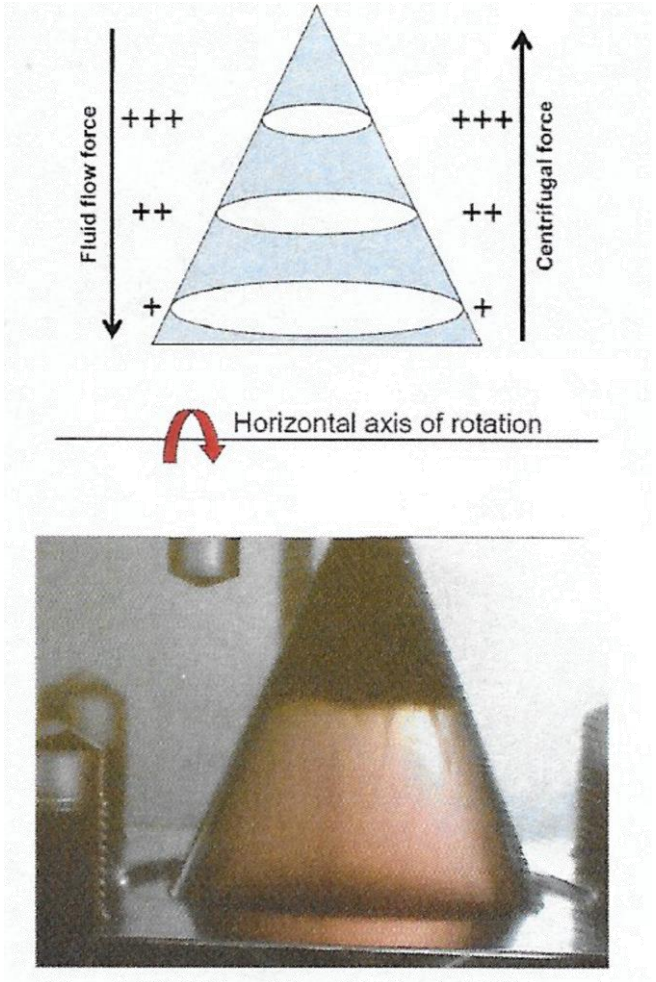
- Settling velocity defined by Stokes' Law:

$$U_s = \frac{2}{9}\frac{(\rho_{cell} - \rho_{fluid})}{\mu_{fluid}} g r_{cell}^{\ 2}$$

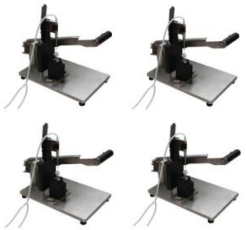
- Countered by fluid velocity through the chamber:

$$U_f = \frac{Q}{A}$$

- Separation occurs when $U_s > U_f$
- Separation based on density, particle size, viscosity, g, flowrate



Vial filling: Challenges increase upon scale up must minimize exposure time to DMSO (cryoprotectant)

	Phase I	Phase II	Commercial
Lot Size	 ~50–100 vials	 ~200–400 vials	 1000+ vials
Filling	 Manual filling	 Parallel filling	 ??Automated filling??
Inspection	 Semi-automated inspection	 Parallel inspection	 ??Automated inspection?? *Inspection for visible particulates is a regulatory requirement for all injectables*

Gaps: Need to enhance pre-freeze stability time or adopt technologies to fill/process 1000+ vials as quickly as 50–200 vials*

Potential CNTY-813 doses per year at launch in existing Century facility

Existing Capacity To Scale to Commercial Production In House



Potential Scale for Commercial

Capable of producing >10,000 doses per year in existing facility without additional suite construction

Assumptions:

- 100–200 L bioreactor scale in multiple suites
- Dose of 800MM cells
- Could produce significantly more doses per year if unfinished space is built for bioreactors

Summary

- Century is developing an iPSC-derived beta islet cell with AlloEvasion™ edits that may reduce the need for immunosuppression
- We are taking a two-pronged approach to scale up the bioreactor process in the PBS vertical wheel as well as in a traditional stirred tank
- We can apply fundamental engineering principles to scale up cell culture, harvest, and filling
- We will leverage experience and learnings from biologics and vaccine fields to achieve successful scale up