Leveraging Fluid Dynamics Characterization to Accelerate Cell Therapy Product Development.

Dr. Tom Heathman, Chief Commercial Officer
Dr. Hamza Patel, Senior Scientist

10th June 2025

The cell therapy industry is facing a crisis of confidence, with investors and partners questioning whether ex-vivo approaches are commercially viable.

Globally, **less than 5%** of patients who could benefit from approved therapies have been able to access them.

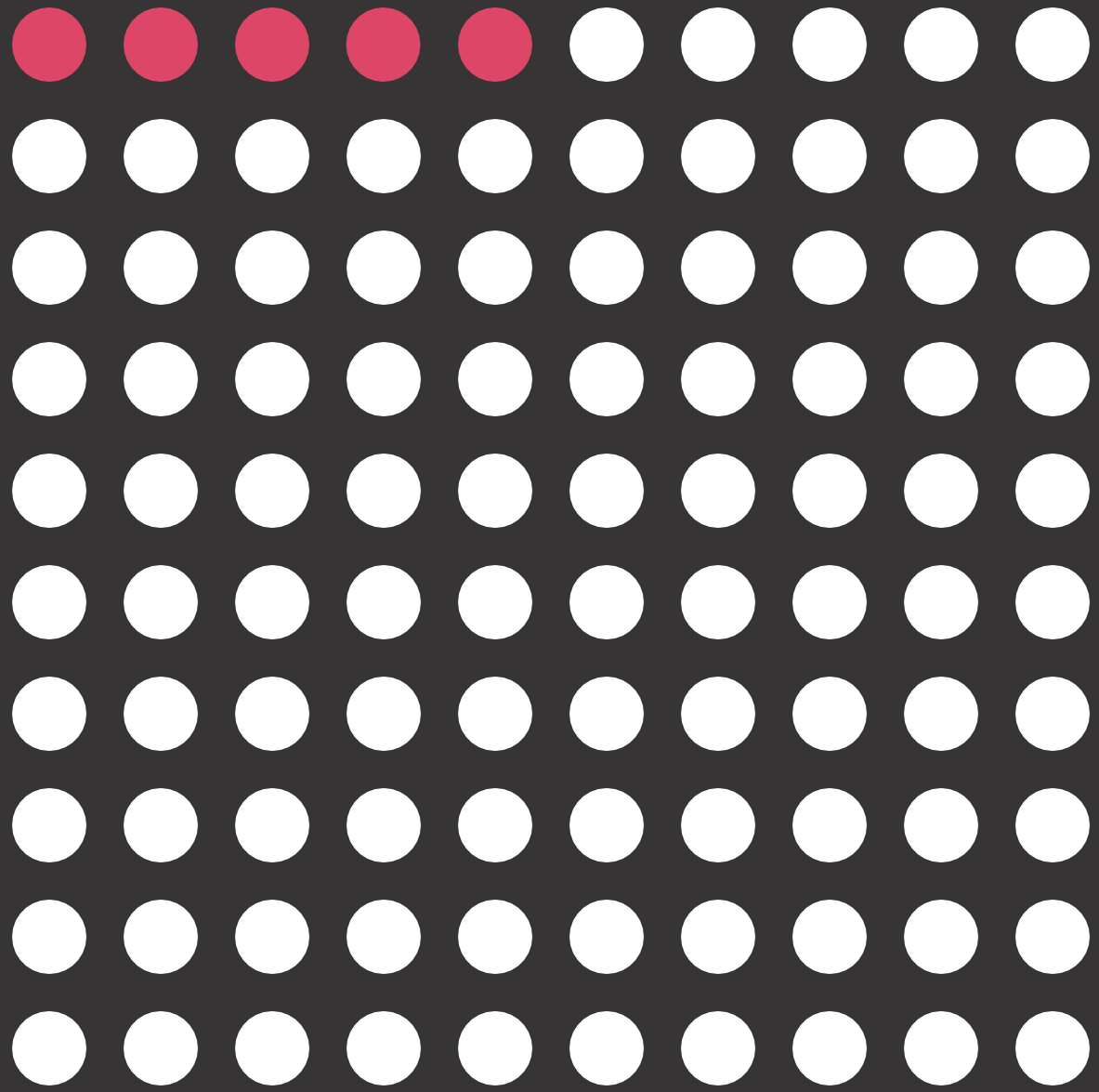
900K*

Addressable Patient Population

~36K

Total Patients Treated

Post 2016 approved products across CAR-T, TCR, and TIL



*Projected : Includes ALL, DLBCL, Multiple Myeloma, CLL and FL. Source: McKinsey, Statnews.
Source: Ori Biotech Internal Research at www.oribiotech.com

Patient Access Reality.

Patient access to these life-saving therapies is currently limited, stemming from manufacturing challenges

Therapy Name	2017	2018	2019	2020	2021	2022	2023	2024	Cumulative Patients Treated by Therapy
KYMRIAH®	13 (Aug 2017)	162	588	999	1,238	1,131	1,072	934 (-13%)	**6,137**
YESCARTA®	19 (Oct 2017)	711	1,225	1,511	1,865	3,111	4,018	3,707 (-8%)	**16,167**
TECARTUS®				119 (Jul 2020)	474	803	996	918 (-8%)	**3,310**
ABECMA®					393 (Mar 2021)	927	1,127	970 (-14%)	**3,417**
BREYANZI®					214 (Feb 2021)	447	815	1,534 (+88%)	**3,010**
CARVYKTI®						290 (Feb 2022)	1,076	2,073 (+93%)	**3,439**
AMTAGVI®								203 (Feb 2024)	**203**
TECELRA®								2 (Aug 2024)	**2**
AUCATZYL®								- (Nov 2024)	**-**
Total Patients Treated per Year	**32**	**873**	**1,813**	**2,629**	**4,184**	**6,709**	**9,104**	**10,341**	**35,685**

Annual Patients Treated with Approved Cell Therapies per Year

Source: April 2025 Ori Data Analytics

"

The **status quo** in cell and gene therapy for most patients today **represents death or serious disability**.

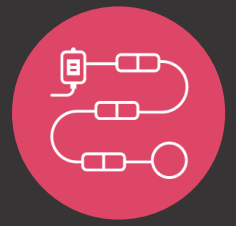
"

Tim Hunt
Chief Executive Officer,
Alliance for Regenerative Medicine (ARM)

What's Holding CGT Back?

Too hard to manufacture

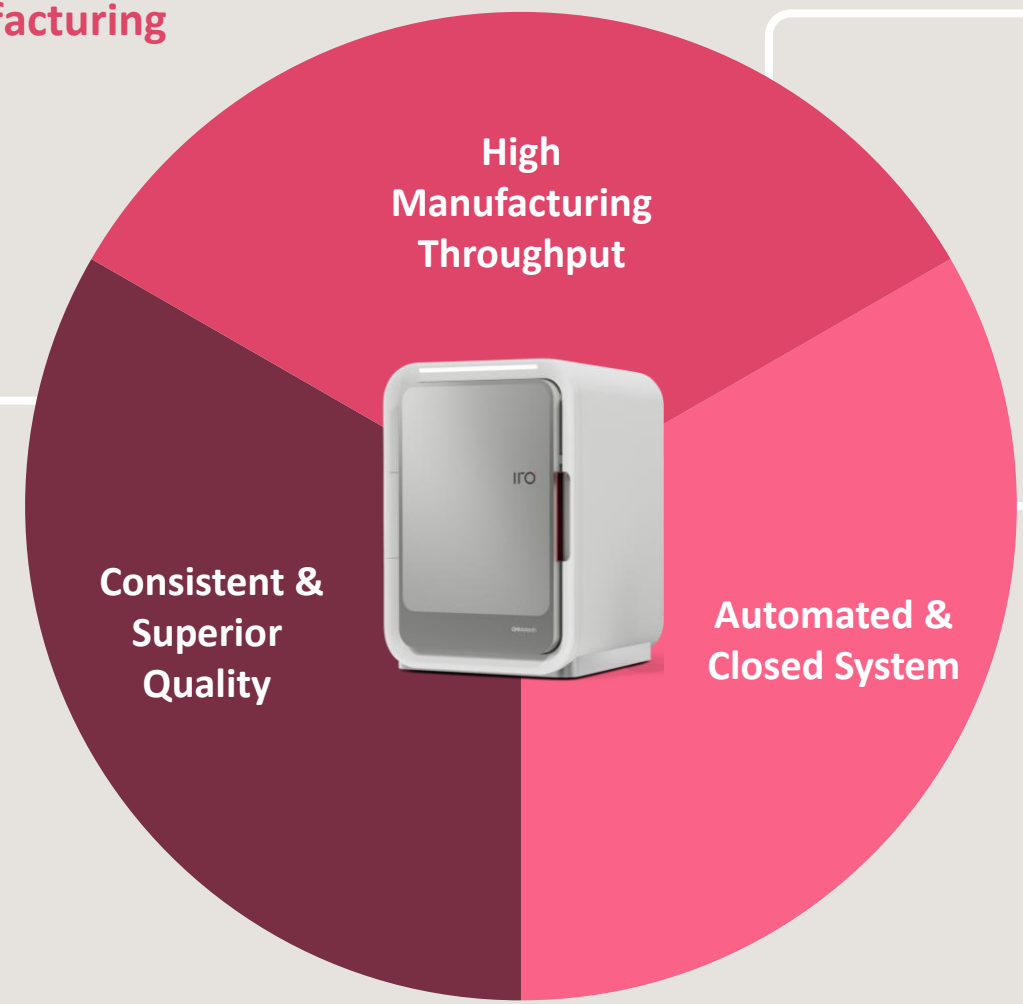
Too expensive to make widely available



Not commercially viable due to **high COGS, low throughput,** and **low reproducibility**

IRO®: The New Standard of Cell Therapy Manufacturing.

IRO **directly addresses** the core requirements in **CGT manufacturing**



Enables **10-50x throughput increase** in the same manufacturing footprint

- Provides ~1000 doses/yr in 1000 sq. ft.
- Lowers COGS 30-50%

Delivers **higher cell quality, higher cell yield,** AND **higher transduction efficiency**

- Shorten process times by 25%
- Lower out-of-spec (OOS) rates to ~5%
- Shorten product development by ~3 years

Automates the most manual part of the workflow, sterile fluid transfer, and representative sampling within a **closed system**

- Reduces human interactions and errors
- Operates in Grade C/D
- Removes all tubing, bags and flasks from your process

You used to have to trade off biological performance for automation. **Not Anymore.**

IRO consistently outperforms first generation manual and automated tools demonstrating strong biological performance alongside the benefits of automation.

IRO is for both R&D and GMP – shortening time to clinic and smoothing the transition to scale

"I expected automation, I expected more process insights, **but I never expected better biological performance right out of the gate.**"

Jason Bock
Co-Founder and Chief Executive Officer, CTMC – A Joint Venture Between Resilience + MD Anderson Cancer Center

Scale to Meet Patient Demand.

- Digitally Connected
- Full Robotic Integration
- Multiplex Capability
- Clinical / Commercial Comparability
- Supports Rapid QA / QC and Release by Exception

We started with **Biology**

>900 Runs

Characterization runs completed (in house and at partner sites in NA and UK)

> 70 Donors / Patients

Testing platform's ability to address donor and patient variability, showcasing the robustness of system outputs across different starting material

11 Unique Processes

Different processes including CAR-T, TCR-T, TILs, CD34+, Dendritic cell based with CAR-M and others on the horizon

12 Partners

5 therapy developers, 5 CDMOs, and 2 AMCs like MD Anderson, Elevate Bio, CTMC, Kincell and Charles River

50ml to 1L

Flexible operating volume range allows activation, transduction and expansion in one bioreactor

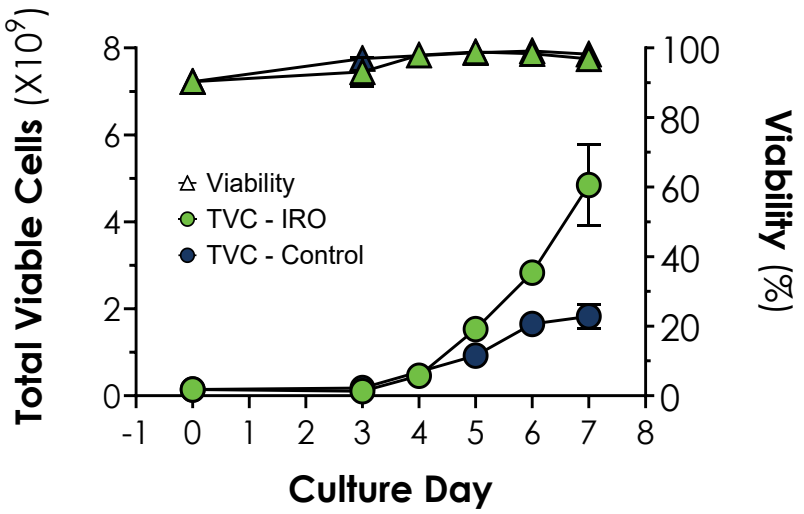
12B Cells

Maximum cell yield observed from bioreactor (~170x fold expansion)

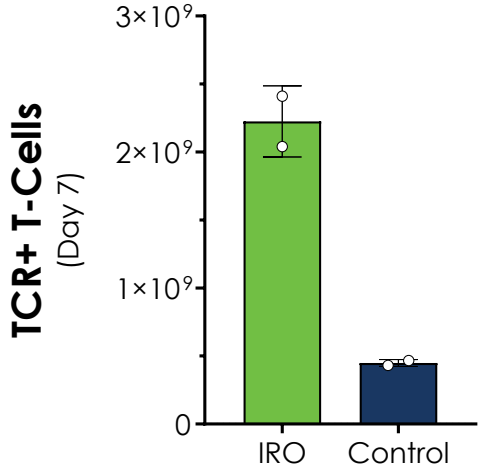
IRO® Evaluation by Elevate Bio: Key Results.

- Elevate Bio performed TCR runs comparing the IRO to an industry standard control at their site.
- After just 3 hours of training, the Elevate Bio team was able to successfully operate and execute the protocol on the IRO platform.
- The IRO data generated by Elevate Bio showed significantly Higher cell yield and Transduction efficiency (~46.3% IRO) compared to the control (~24.7%).
- All other analytical results were comparable: viability, CD4/CD8 ratio and memory, activation and exhaustion panels.

Total Viable Cells
IRO vs Static Control



Transgene+ T-Cells at Harvest
IRO vs Static Control



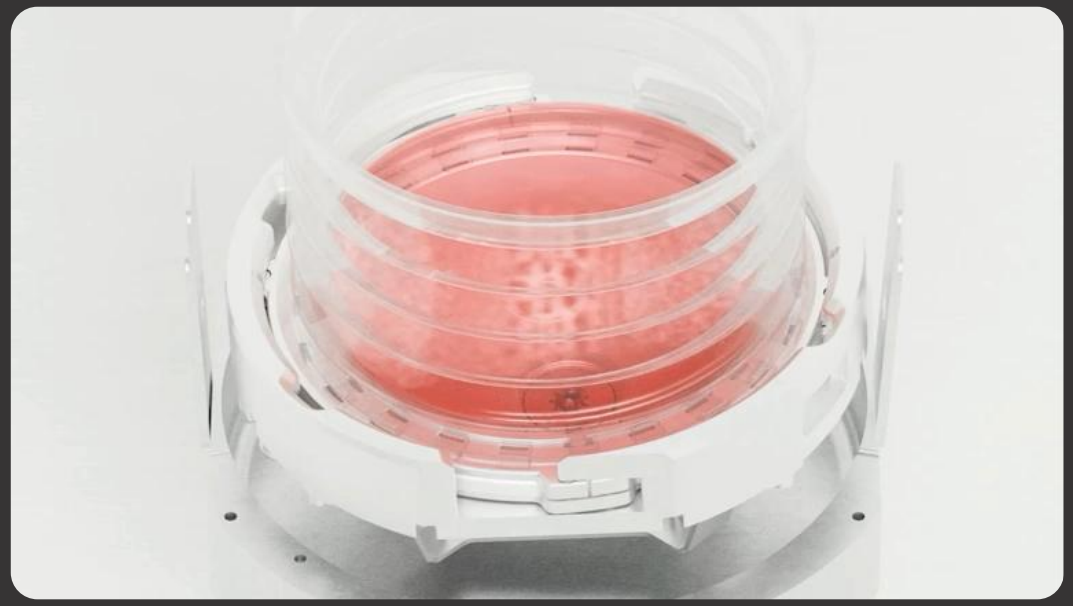
"The IRO's intuitive design streamlines training and operation, **enabling rapid adoption and immediate productivity.**"

Jeff Cram
Senior Director, Cellular Process Development

Why do we see better cell yields and transduction efficiency in IRO?

The Bellows Bioreactor

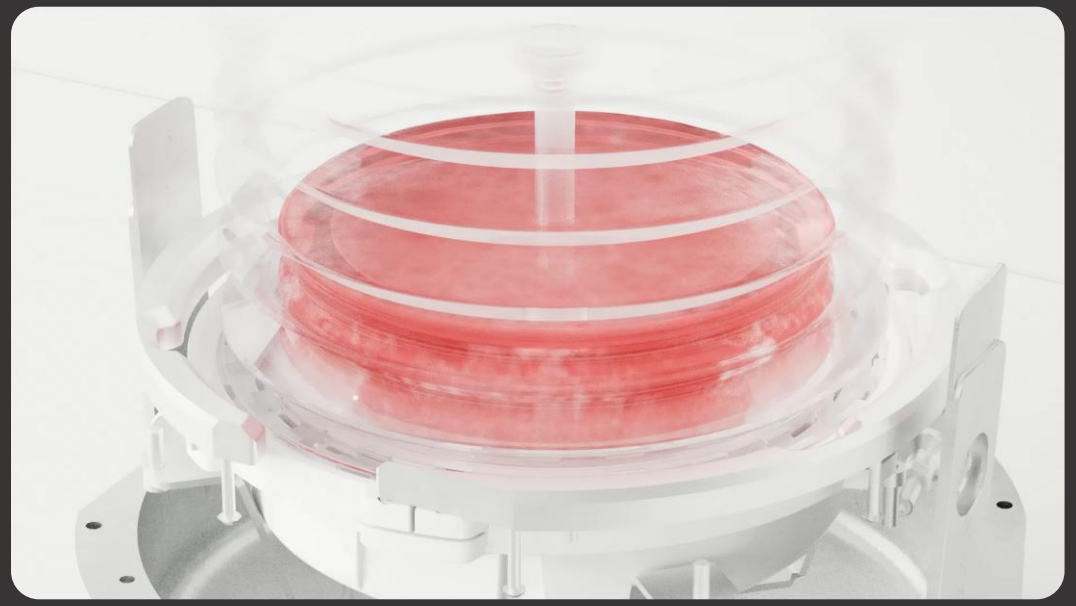
Rock Mixing



Operating parameters

- Agitation rate
- Rock angle
- Base height

Compression Mixing



Operating parameters

- Agitation rate
- Stroke length
- Base height

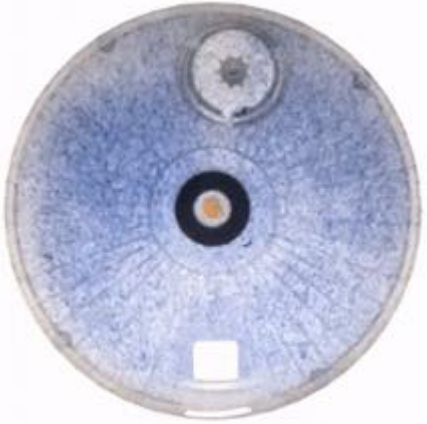
Engineering Mixing Characterization.

Ori has developed mixing characterization experimental tools to accelerate biological process characterization and optimization

Mixing Time

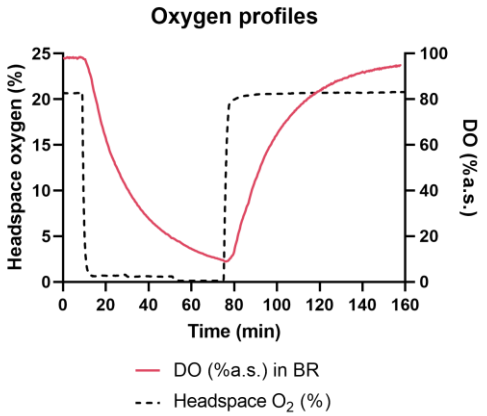
Quantifies time to reach homogenous culture environment ensuring equal distribution of nutrients and oxygen

Particle Suspension



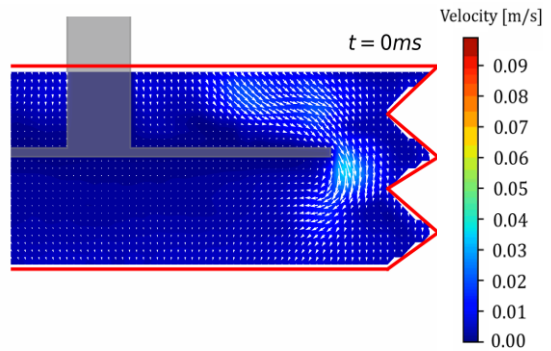
Quantifies the level particle suspension to enable control over mixing regimes during different process phases

Oxygen Mass Transfer



Quantifies the efficiency of oxygen transfer, which is essential for sustaining healthy cell cultures

Velocity and Shear

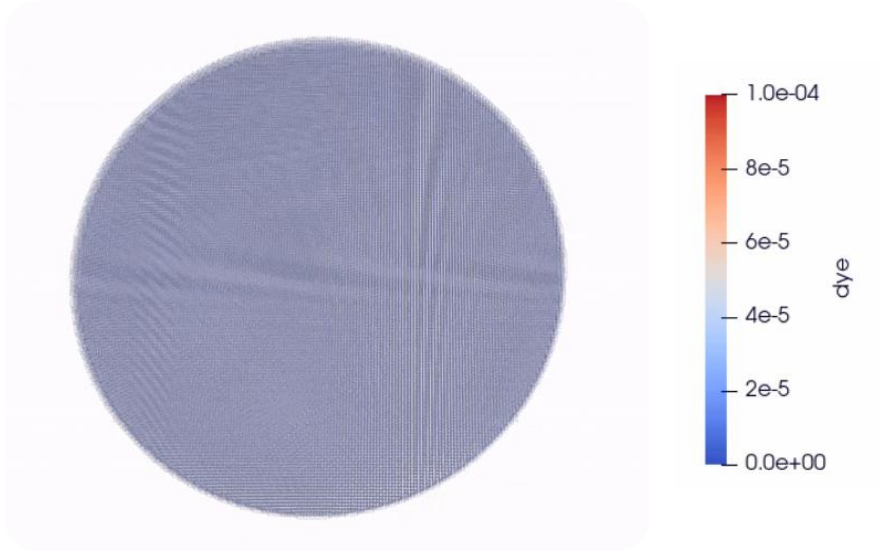


Particle Image Velocimetry (PIV): Measures fluid velocities, providing insights into flow patterns and shear stress which influences cell health

Engineering Mixing Characterization.

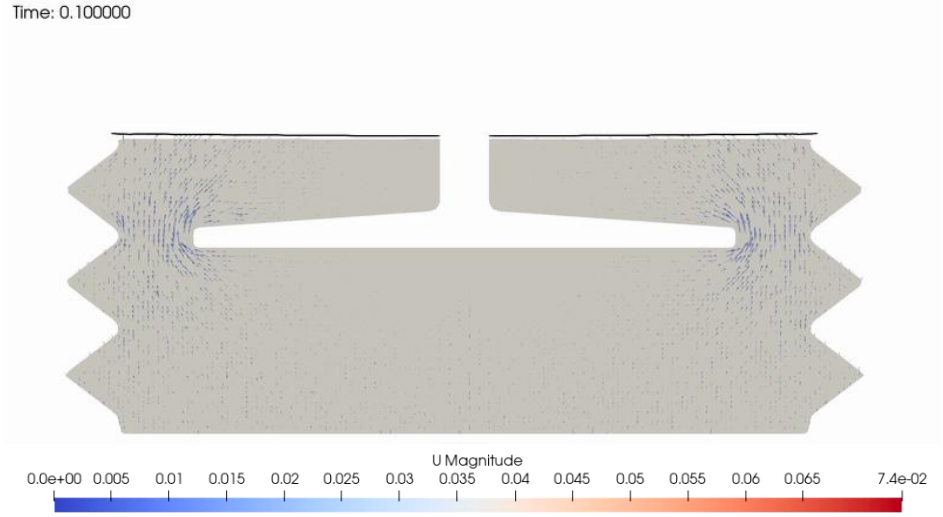
Complementing experimental tools with computational fluid dynamics (CFD) to streamline biological process characterization and optimization

Mixing Time



Mixing mode: Rocking
Low volume

Velocity and Shear



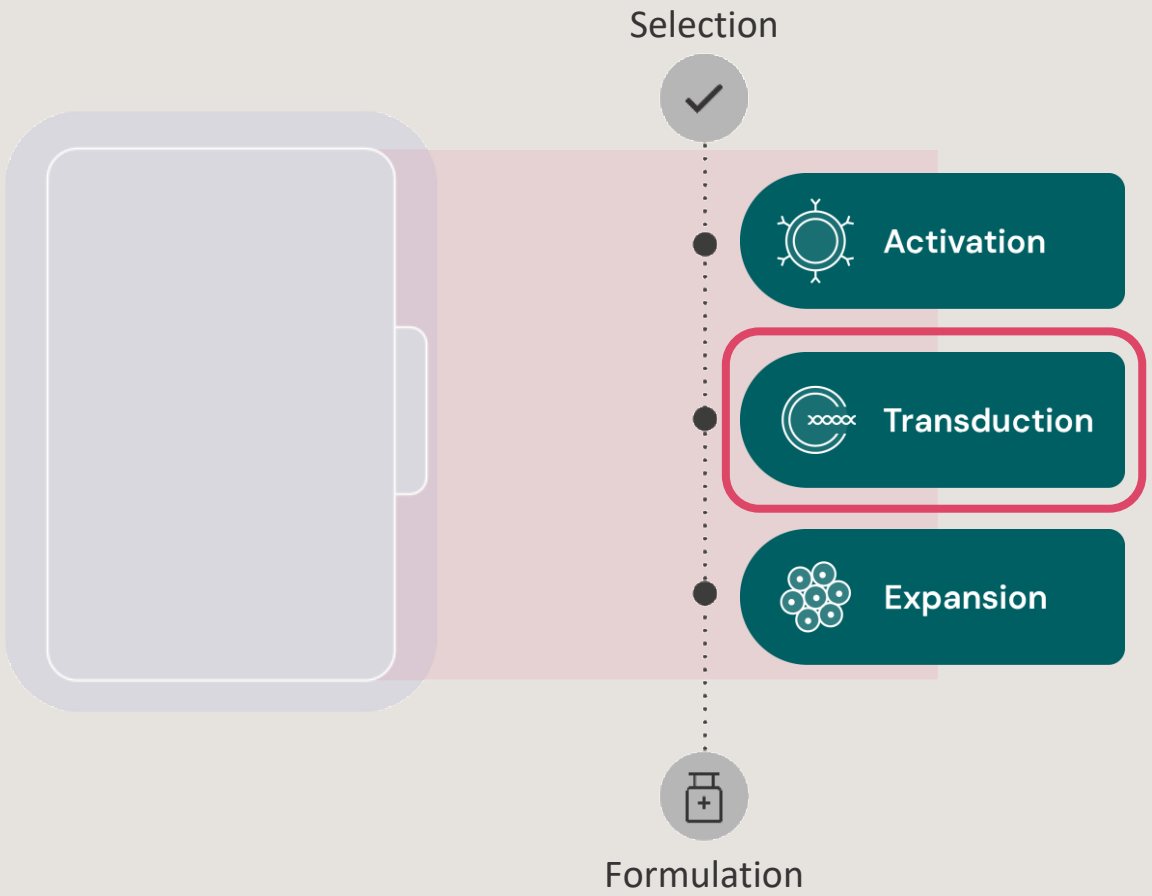
Mixing mode: Compression
High volume

Case Study One.

Early Process: Transduction

Standard CAR-T Manufacturing Process.

Leveraging customized mixing in IRO to enhance transduction efficiency

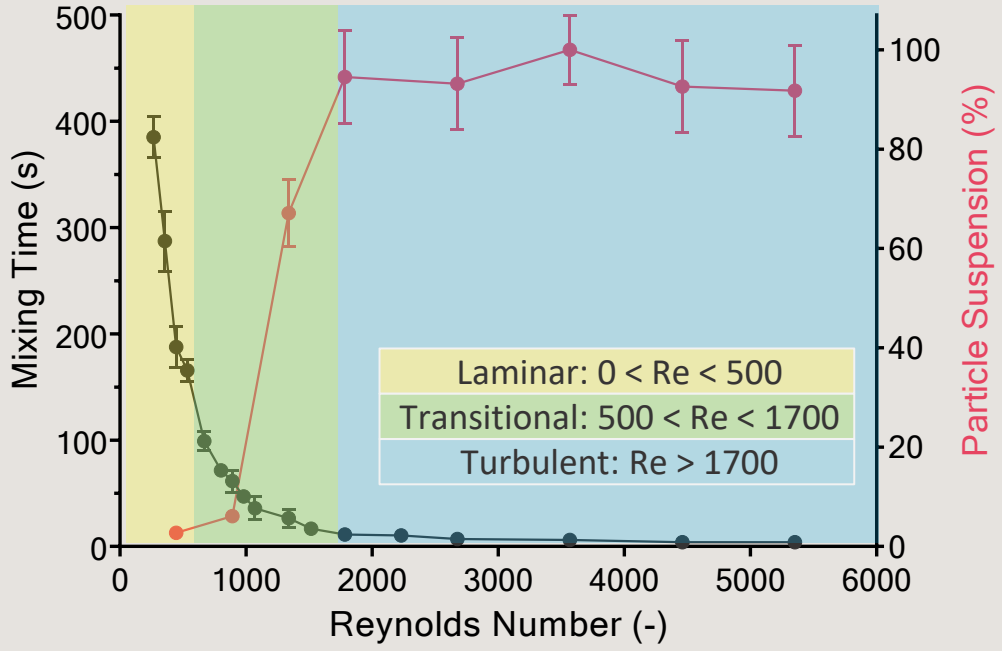


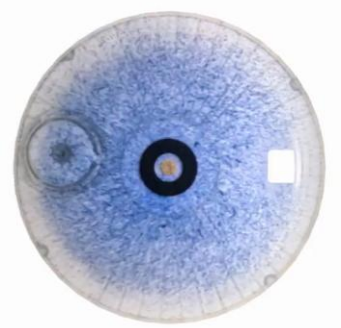
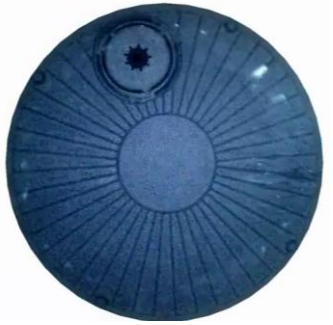
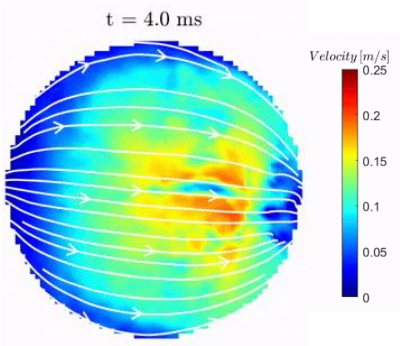
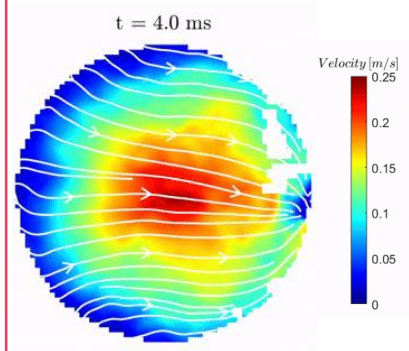
- Static culture results in dispersed cell settling, leading to limited virus-to-cell and cell-to-cell contact
- Optimize mixing to:
  - Increase virus-to-cell contact → higher probability of successful gene delivery
  - Increase cell-to-cell contact → enhanced T cell activation → activated T cells in a more favorable state for virus uptake
  - Minimize shear exposure → reduced mechanical damage to cells and virus

Customized Mixing in IRO to Enhance Transduction.

Using fluid dynamics tools to identify optimal mixing regime for transduction

Characterising Mixing Time and Particle Suspension During Low Volume Rock Mixing

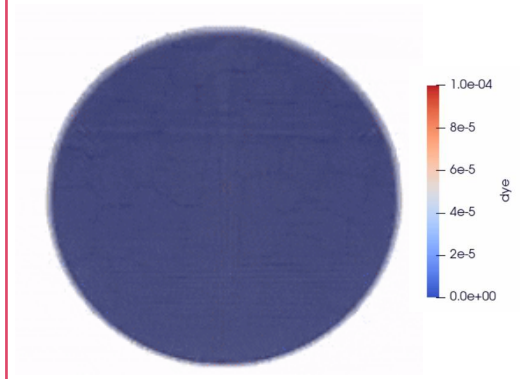
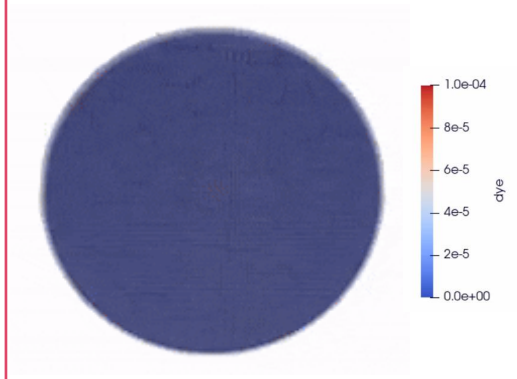


	Transitional Mixing Regime	Turbulent Mixing Regime
Increase virus-to-cell contact → Short mixing time	Mixing time: Short (10s – 100s)	Mixing time: Very short (<10s)
Increase cell-to-cell contact → Local cell concentration	Local particle concentration 	Uniform particle suspension 
Minimize shear exposure → Low fluid velocities and shear stress	Low fluid velocities = low shear 	High fluid velocities = high shear 

Customized Mixing in IRO to Enhance Transduction.

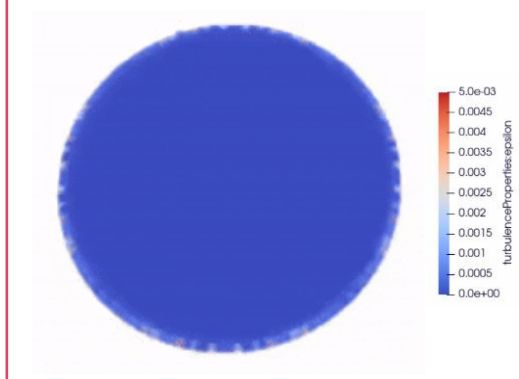
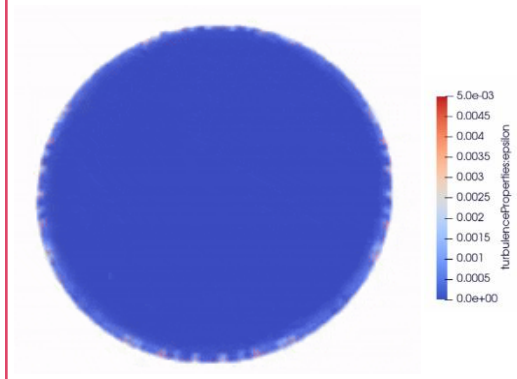
Comparing mixing regimes using computational fluid dynamics (CFD)

Mixing Time

Mixing Parameter 1 (Transitional Regime)	Mixing Parameter 2 (Turbulent Regime)
	

Mixing mode: Rocking
Low Volume

Velocity and Shear

Mixing Parameter 1 (Transitional Regime)	Mixing Parameter 2 (Turbulent Regime)
	

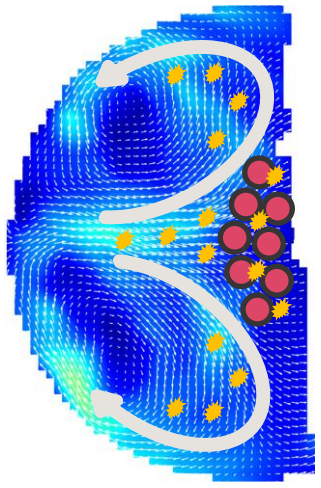
Mixing mode: Rocking
Low Volume

Customized Mixing in IRO to Enhance Transduction.

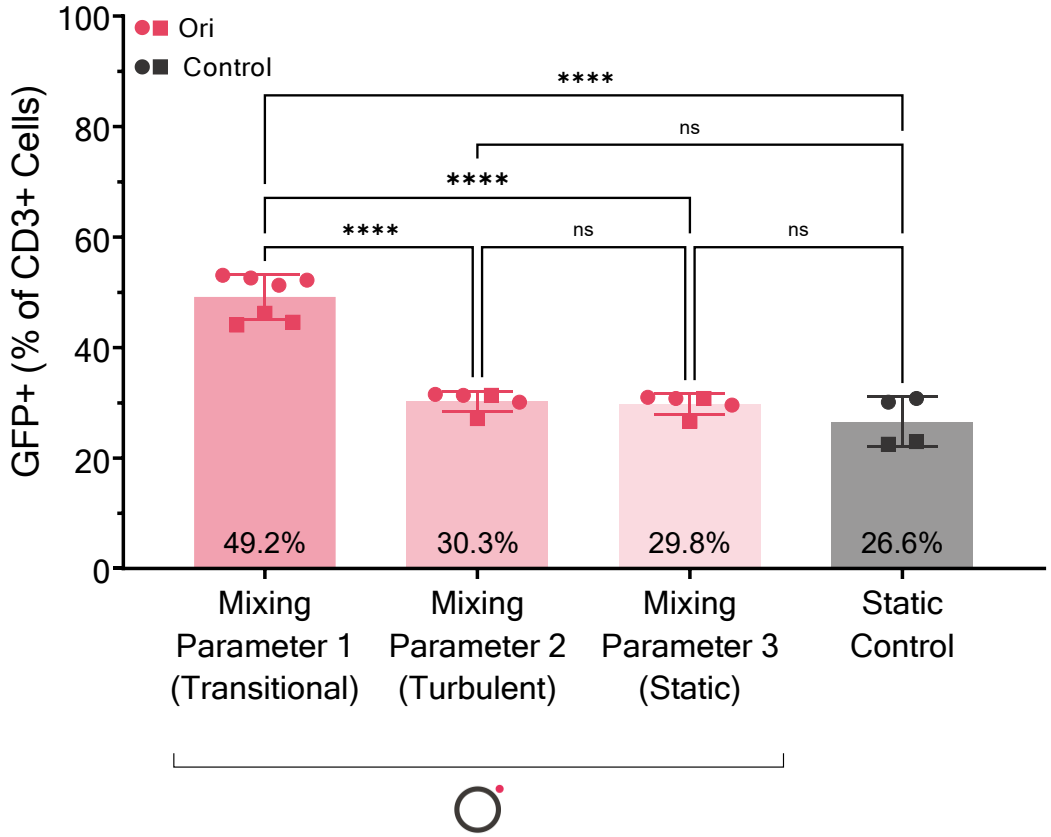
Gentle mixing in IRO enhances transduction efficiency

- Gentle recirculation of the media → increase virus-to-cell contact
- Solids concentration → increase cell-to-cell contact
- Low fluid velocities → minimise shear damage to cells and virus
- Outcome: significantly improved transduction efficiency

Vector Recirculation + Cell Concentration



Enhancing Transduction Efficiency using Customized Mixing in IRO



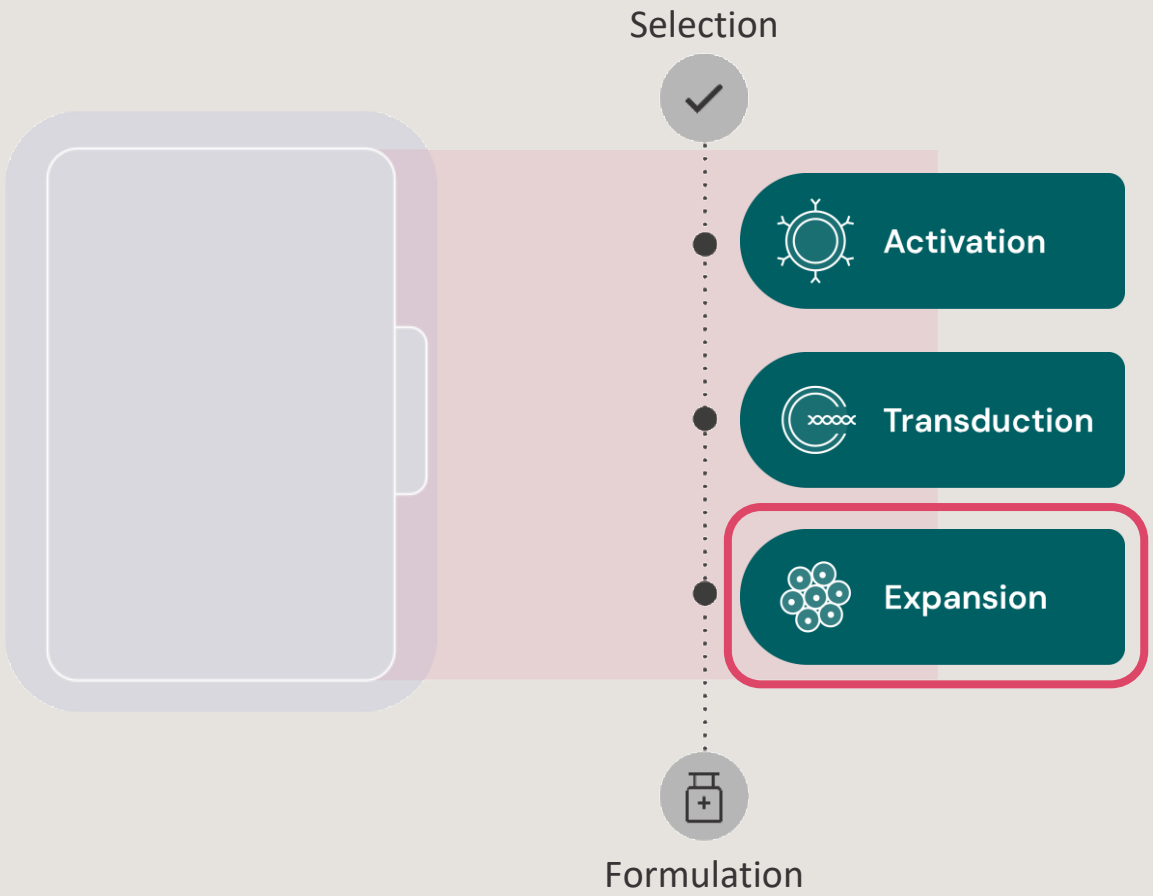
Note: Circle and square symbols represent two healthy T cell donors; MOI=0.5; Statistical significance was determined using one-way ANOVA ($\alpha = 0.05$). Asterisks indicate significant differences ($p < 0.05$).

Case Study Two.

Late Process: Expansion

Standard CAR-T Manufacturing Process.

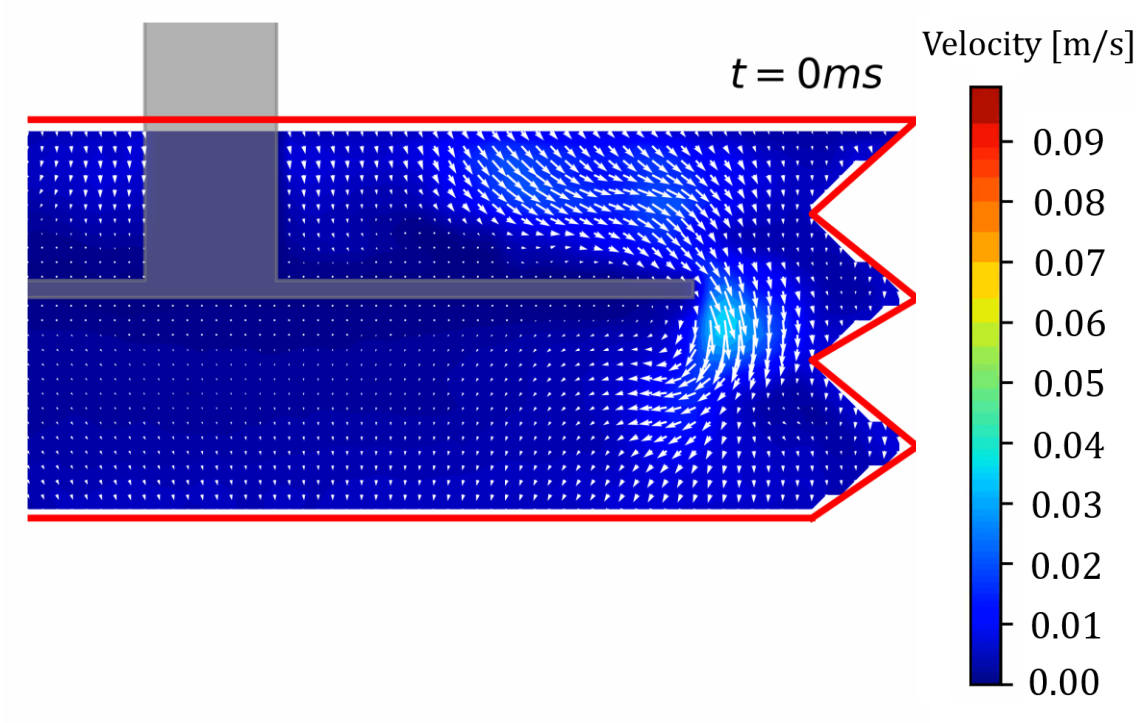
Leveraging customized mixing in IRO to enhance T cell expansion



- As volume and cell density increase, static and rocking modes are limited in their ability to sustain suspension and deliver sufficient oxygen and nutrient transfer
- Compression mixing better suited to sustain exponential growth during the expansion phase
- Optimize mixing to:
  - Promote high mass transfer
  - Keep cells in suspension
  - Minimize shear exposure

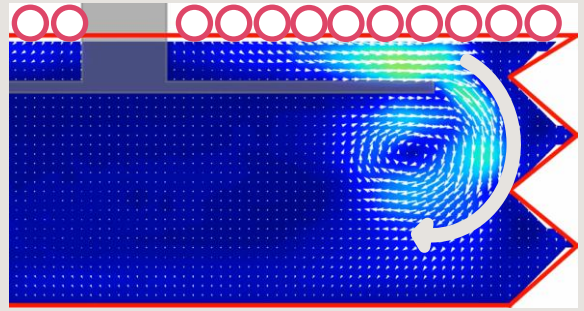
Customized Mixing in IRO to Enhance T Cell Expansion.

Characterising flow field during compression mixing using particle image velocimetry (PIV)

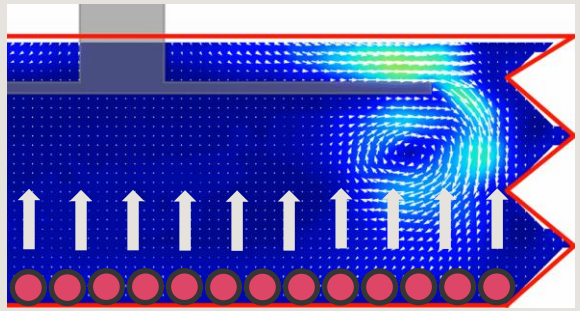


A vortex is formed during the down stroke underneath the baffle and is essential in the transfer of oxygen from the headspace and keeping cells in suspension

Oxygen Mass Transfer



Cell Resuspension

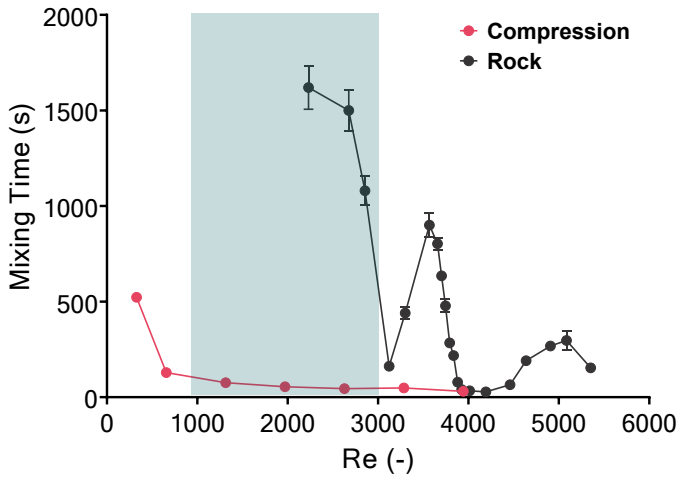


Customized Mixing in IRO to Enhance T Cell Expansion.

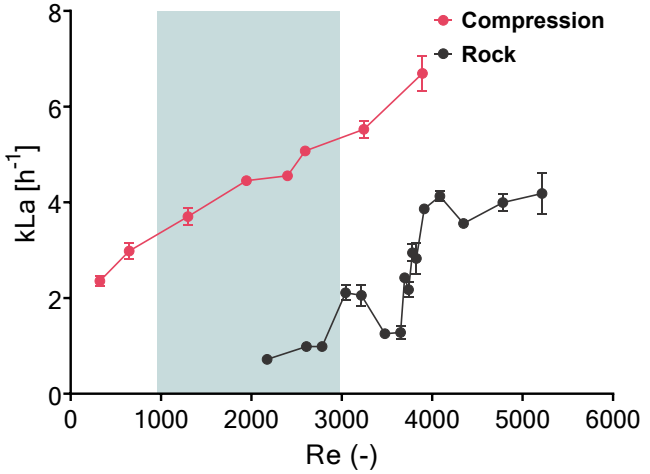
Comparing mixing time and oxygen mass transfer profiles during rock and compression mixing at high volumes

- Compression mixing is fully turbulent at low agitation rates
- The vortex produced by the baffle during compression mixing results in high mass transfer even at low agitation rates
- The mixing time and oxygen mass transfer for rock is fluctuating, indicating resonance phenomena, characteristic for rocking and shaken systems

Mixing Time During High Volume Rock and Compression Mixing



Oxygen Mass Transfer During High Volume Rock and Compression Mixing



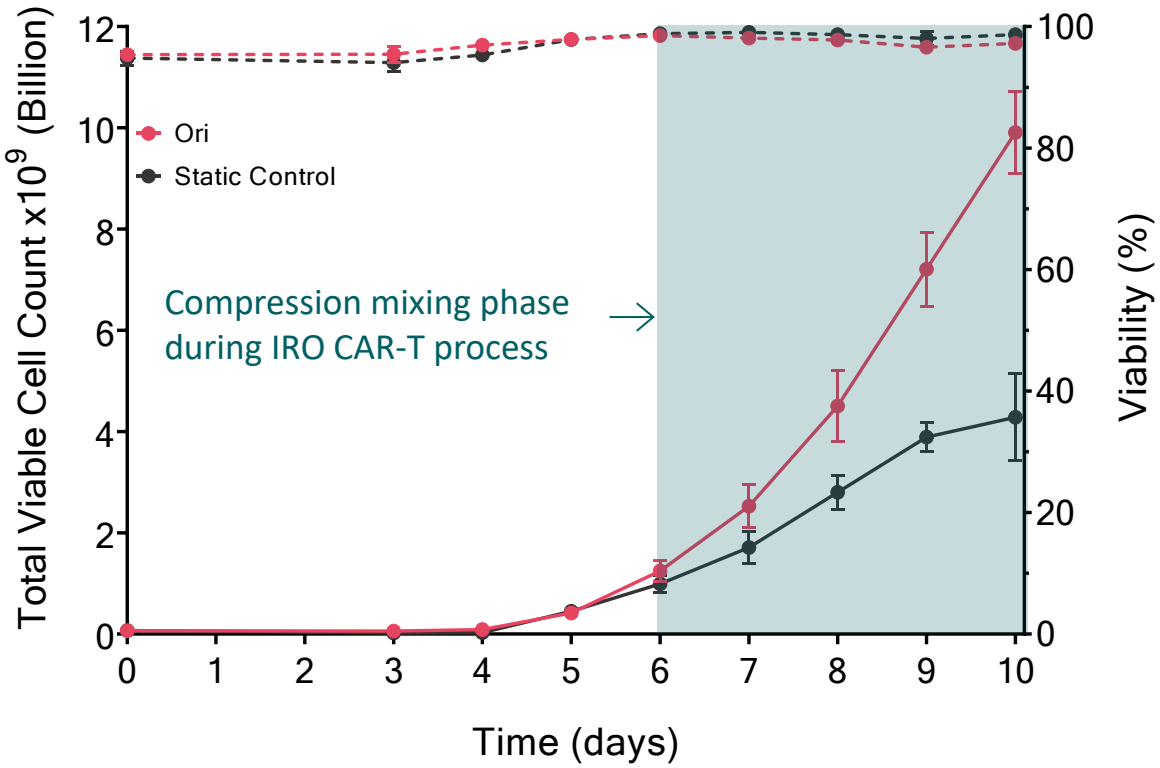
Note: green shaded region = good mass transfer and low shear during compression mixing

Customized Mixing in IRO to Enhance T Cell Expansion.

Compression mixing in IRO is well-suited to sustain exponential growth during expansion phase

- Micro-scale mixing due to turbulent compression → high oxygen mass transfer
- Trailing vortex produced by the baffle → effective solids resuspension
- Outcome: significantly improved growth kinetics

Cell Growth and Viability Profile



Note: Data shown for 24 runs, 6 donors

Transduction Mixing.

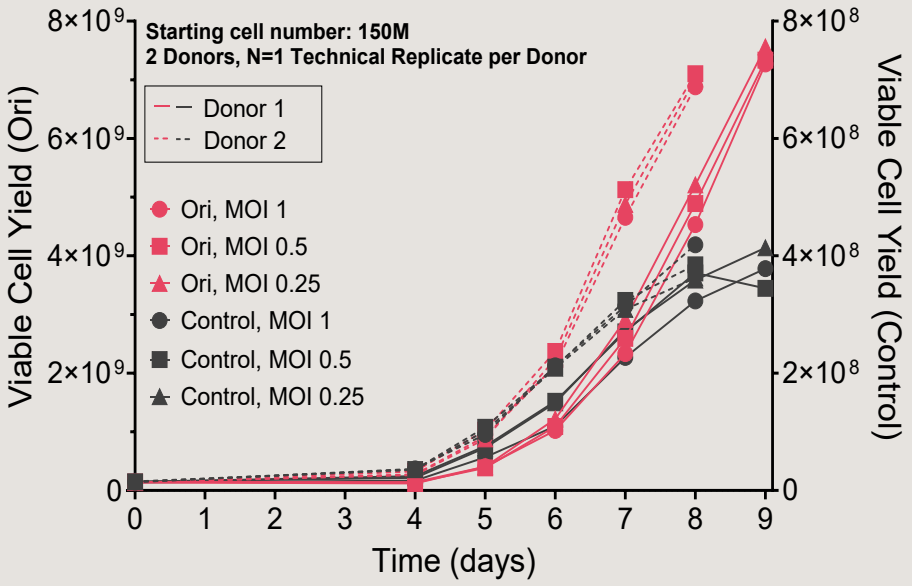
CD19 CAR MOI Titration Study

CD19 CAR-T Data - Different MOIs

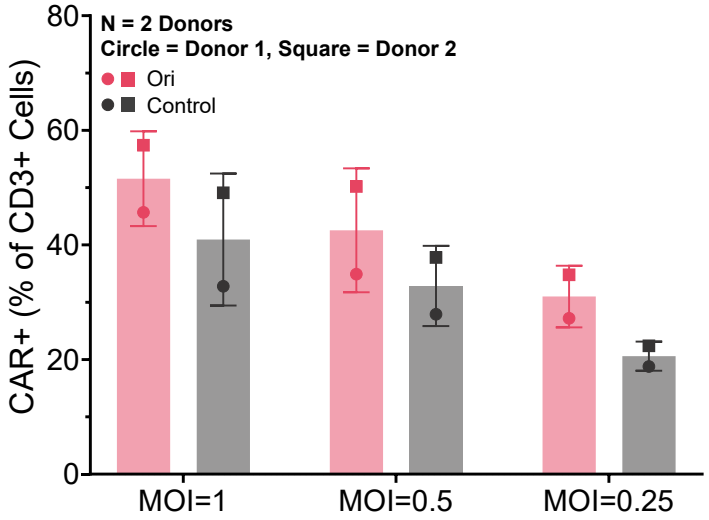
Key Takeaways

- Higher transduction efficiency was observed in Ori compared to the control across the tested Multiplicity of Infections (MOIs)
- Higher yield of CAR-T cells was achieved in Ori platform using MOI 0.5 compared to the control using MOI 1.0. This demonstrates the possibility of reducing the virus needed to achieve a target CAR-T yield and ultimately reducing cost of goods

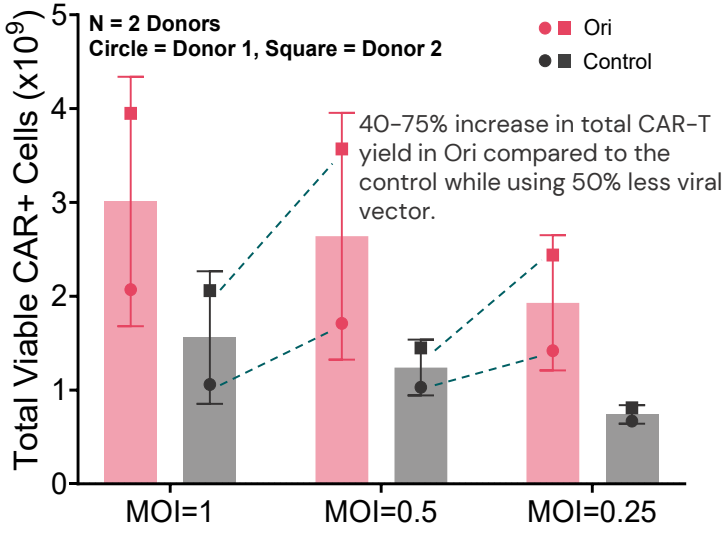
Cell Growth Profile



Transduction Efficiency



Total CAR-T Yield (Day 8)



Note: MOI: ratio of infectious virus particles to cells.

Key Takeaways

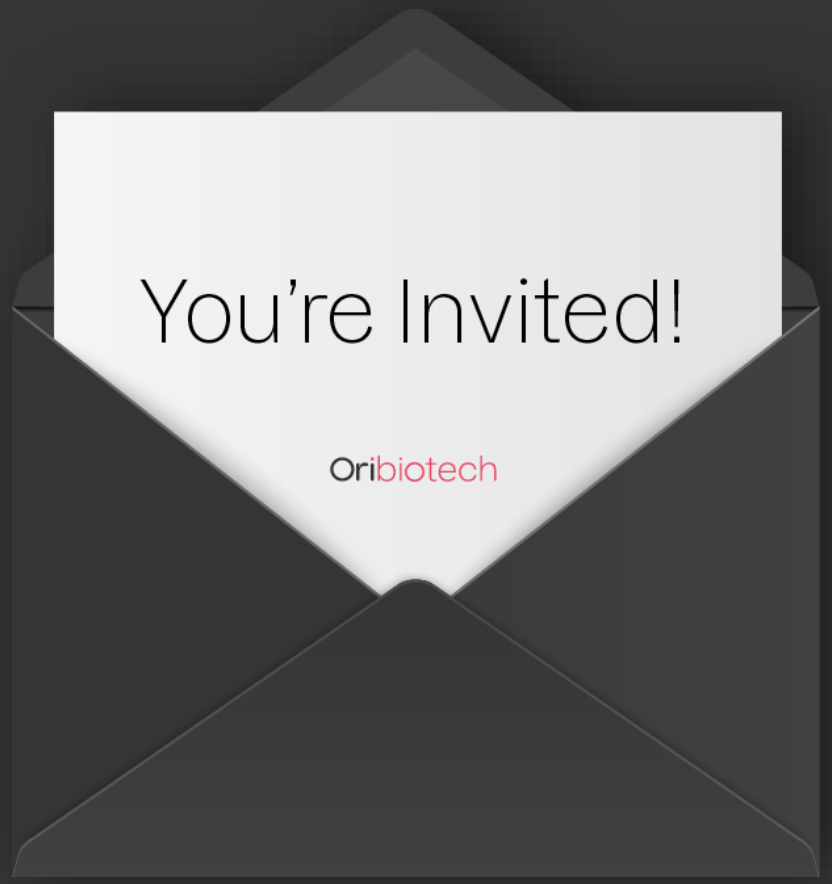
We are employing Fluid Dynamics Characterization in IRO to unlock critical benefits for our partners

Deploying methods for deep engineering characterization of cell manufacturing technologies is the next key inflection for the effective development of cell and gene therapy products

Reducing product development timelines for our partners - We have developed these mixing characterization experimental tools to accelerate biological process characterization and optimization using our IRO manufacturing technology

Massively reducing the cost of viral vector for our partners - We have identified the optimal mixing regime for cell transduction, delivering almost 2x the transduction efficiency in IRO compared to a static control

Reducing process length by 2 days for our partners - We have identified the optimal mixing regime for cell growth, delivering more than 2x the viable cell number in IRO compared to a static control



Want to learn more?

- Book a demo of the IRO Platform
- Schedule a Lunch & Learn at your site
- Visit our labs in the US or UK

We're looking forward to helping you enable widespread patient access to life saving cell and gene therapies.

contact@oribiotech.com

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