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Engineering iPSCs with Synthetic Receptors to Drive Differentiation Compatible with Scale-Up

Teisha Rowland, Ph.D.
Principal Scientist
Umoja Biopharma

Umoja Biopharma

- **Innovative multi-platform immuno-oncology company focused on curative, "off-the-shelf" *in vivo* and cell therapies for solid tumors**

> **"Our approach is scalable and flexible – we aspire to create immunotherapies that are accessible and valuable for patients across the full range of solid tumors."**
>
> **– Andy Scharenberg, CEO Umoja Biopharma**

- **Four complementary technology platforms designed to address the key limitations of current CAR T-cell therapies:**
  - **VivoVec (ARM *in vivo*)**: Gene therapy product with scalable manufacturing – designed to enable *in vivo* CAR T-cell generation
  - **RACR/CAR (EXPAND)**: Cytokine signaling system could obviate lymphodepletion while enhancing potency and persistence
  - **TumorTag (TARGET)**: Combinatorial targeting of the tumor and its microenvironment to address tumor heterogeneity, antigen escape and immunosuppression applicable across tumor types
  - **Engineered iPSCs (ARM *ex vivo*):** iPSC-derived, gene engineered allogeneic, "off-the-shelf" immune cell therapy platform.

Umoja Biopharma's Engineered Allogeneic Therapies Team

Leadership

Ryan Larson, PhD
Vice President
Head of Immunology
Previous: Senior Director at Bristol Meyer Squibb
Training: PhD and Post-Doc Univ of Washington Immunology

Teisha Rowland, PhD
Principal Scientist, Co-Lead
iPSC Team Lead
Previous: Director of CU Boulder Stem Cell Center
Training: PhD UC Santa Barbara

Sam O'Hara, PhD
Principal Scientist, Co-Lead
Allogeneic Research Lead
Previous: As. Principal Scientist at Merck – Cambridge Exploratory Science Center
Training: PhD CU Boulder

Cassidy Arnold
Engineer, iPSC Team
Previous: Regenerative Patch Technologies
Training: BS UC Santa Barbara

Ryan Koning
SRA, Immunology & Gene-Editing
Previous: Dr. Mike Jensen's Lab at Seattle Children's Research Institute
Training: BS University of Washington

Dave Vereide, PhD
Senior Scientist
Gene Editing Lead
Previous: Jamie Thomson's Lab at Morgridge Institute for Research
Training: PhD University of Wisconsin

Ashley Yingst, MS
Scientist, iPSC Team
Previous: Dr. Michael Verneris's lab at CU Denver
Training: MS Des Moines University

Dillon Jarrell, PhD
Scientist, iPSC Team
Previous: Jeffrey Jacot's lab at CU Denver
Training: PhD CU Denver

Pipeline: technologies integrated to create therapies

Therapeutic Clinical Development

Candidate *Target*	Platforms	Indication	Preclinical	Phase 1	Late-Stage Development	Upcoming Milestones
UB-VV200 *Multiple/ in vivo TIL*	VIvoVec + RACR/TagCAR *TumorTag/UB-TT170*	Solid Tumors (gyn malignancies)				IND as soon as 2023 ENLIGHTen enrolling
UB-VV100 *CD19*	VivoVec + RACR/CAR (CD19 CAR)	Hematologic Malignancies				Pre-IND 8/22 IND as soon as 2023
UB-iC200 *Multiple*	iCIL Cell + RACR/TagCAR *TumorTag/TBD*	Solid Tumors				IND as soon as 2024 IND as soon as 2024

TumorTag Clinical Development

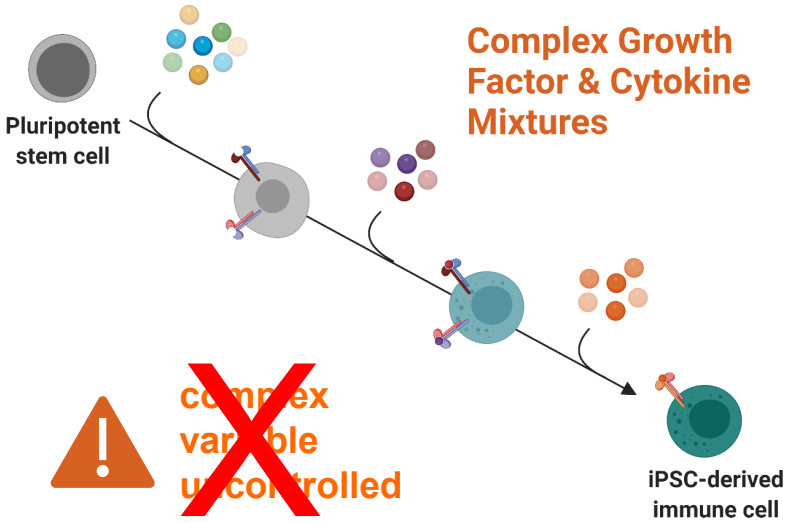
Target	Platforms	Indication	Preclinical	Phase 1	Late-Stage Development	Upcoming Milestones
UB-TT170/*FR*	*TumorTag*	ENLIGHTEn (osteosarcoma)				ENLIGHTen enrolling
PSMA	*TumorTag*					
CA IX	*TumorTag*					
FAP	*TumorTag*					
Ag-independent	*TumorTag*					

Umoja is developing an "off-the-shelf," engineered iPSC cell therapy platform to address key challenges in allogeneic cell therapy:

- Eliminating lymphodepletion and enhancing *in vivo* persistence of cells
- Reducing manufacturing complexity, cost, and variability to make *better* cells

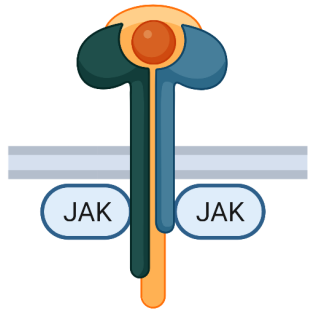
Key Cytokines are Required for *ex vivo* Cell Manufacturing and *in vivo* Persistence of iPSC-Derived Immune Cells

Cell Manufacturing



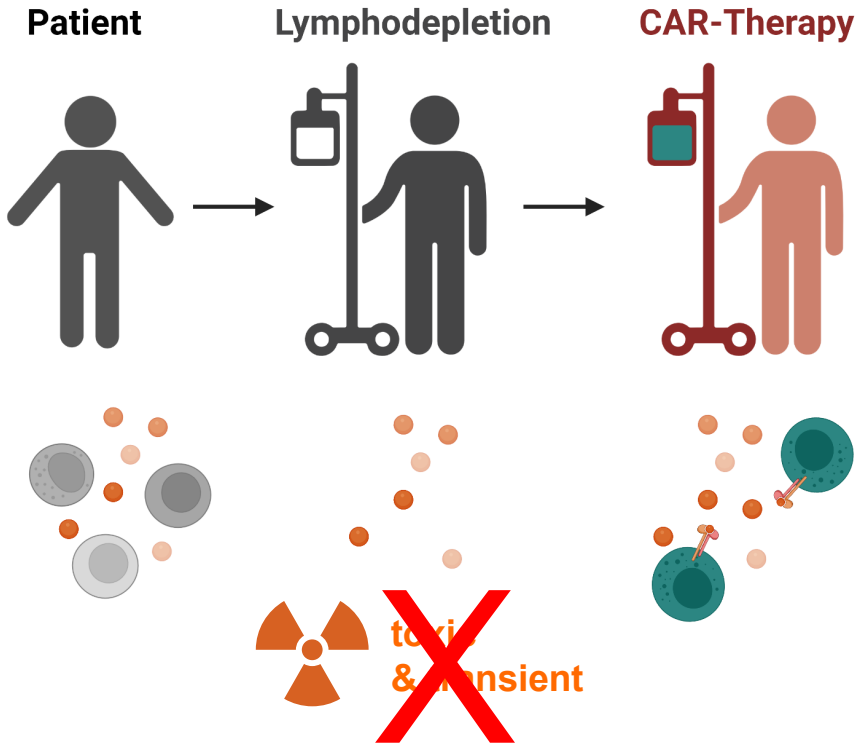
Common Gamma Chain Cytokines

IL-2
IL-15
IL-7
IL-21



Cell Activation & Proliferation

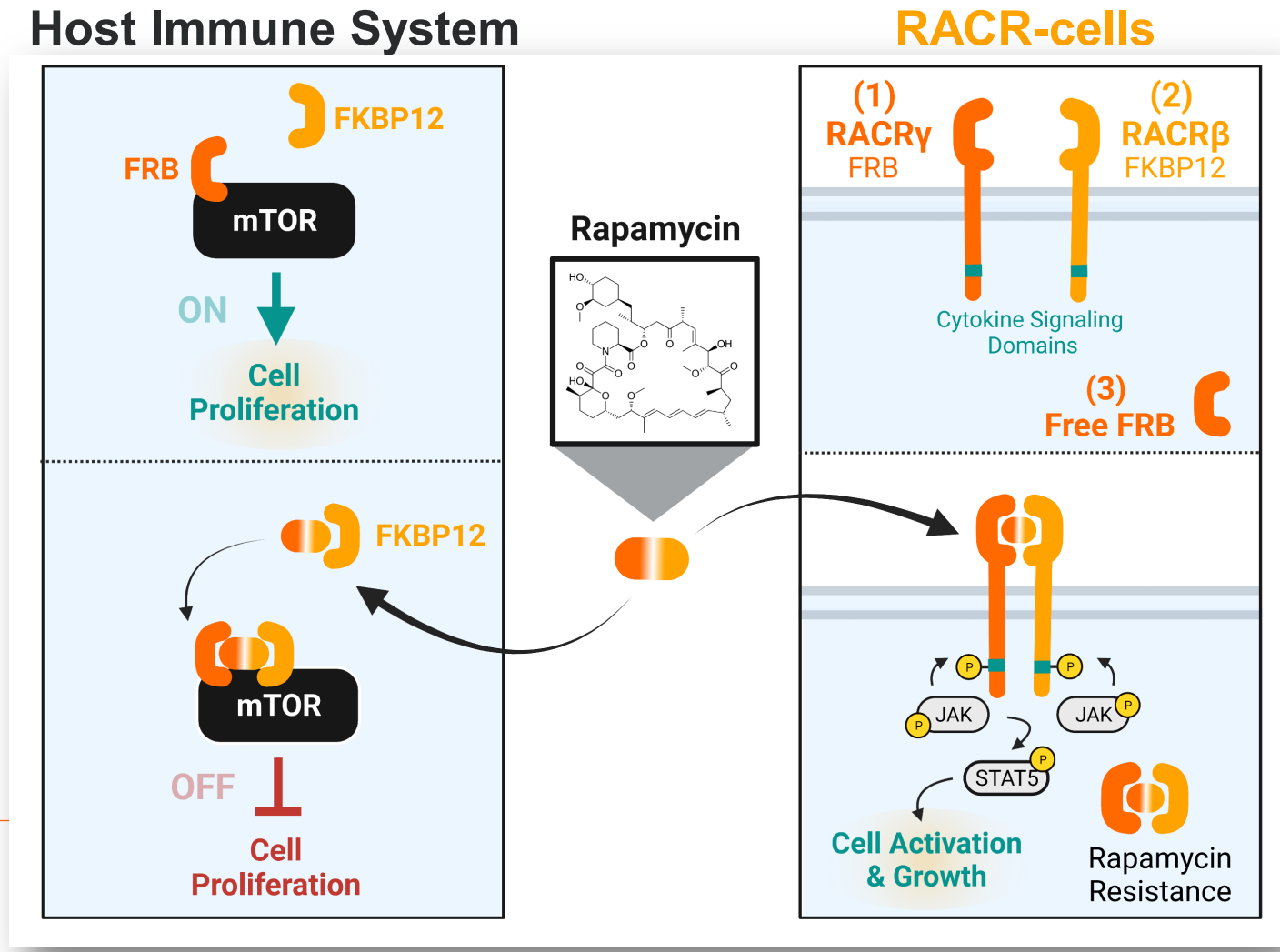
In Vivo Persistence



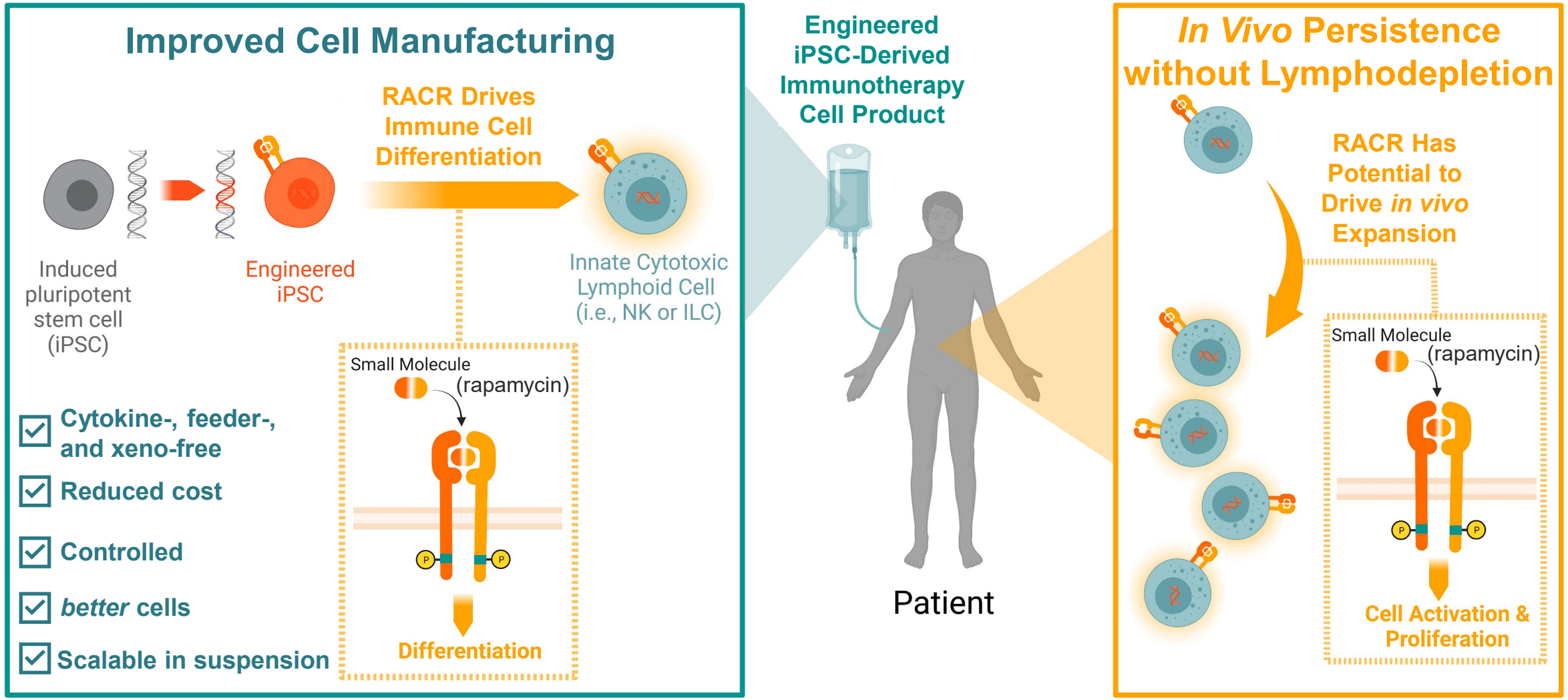
Improving iPSC Differentiation and Overcoming Lymphodepletion with RACR:
Rapamycin Activated Cytokine Receptor

EXPAND

- Rapamycin is an FDA approved small molecule immunosuppressant, functioning by inhibiting mTOR (left).
- Upon rapamycin binding, RACR activates JAK/STAT5 (IL-2/IL-15) signaling to drive cell activation & proliferation (right).
  → **Selective activation and proliferation of engineered cells**
- RACR also includes free intracellular FRB to provide rapamycin resistance to the engineered cells, while host immune cells are suppressed



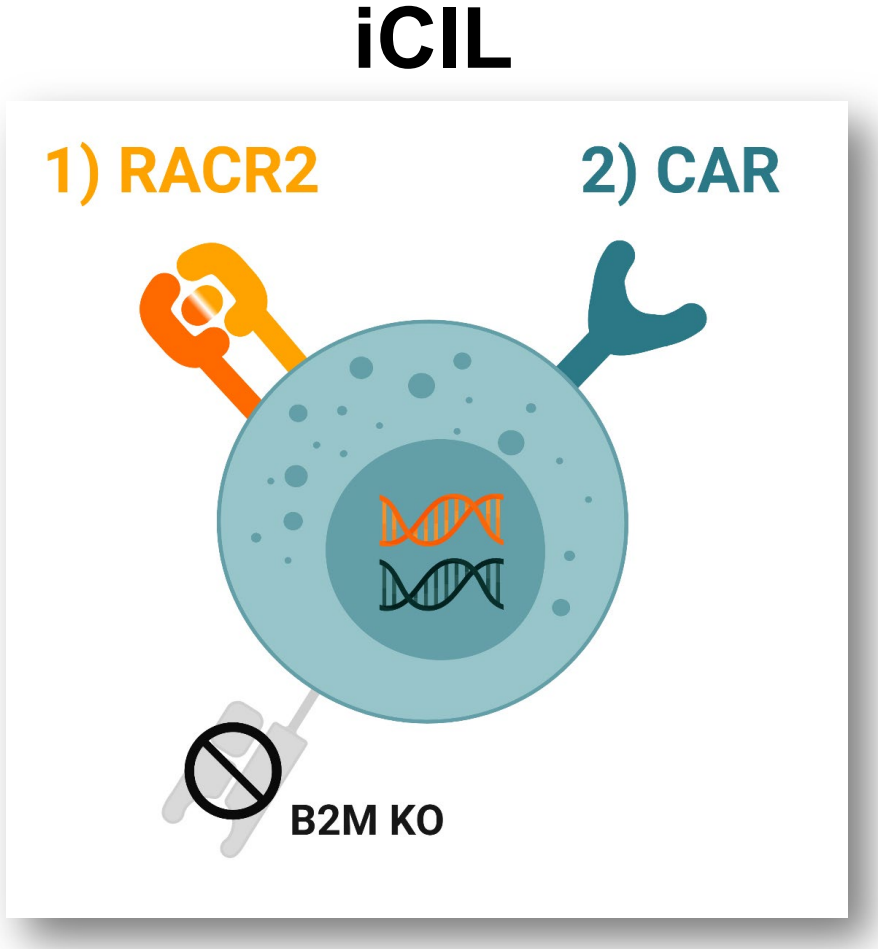
RACR: Engaging a Synthetic Cytokine Receptor for Cell Therapy Products



Synthetic iPSC-Derived Cytotoxic Innate Lymphocytes (iCILs) as Off-the-Shelf Cell Therapeutic Platform

ARM

Criteria	Therapeutic cell
Clinical Target	Solid & hematologic malignancies
CAR	Fixed specificity or universal TagCAR
Gene Edits	**1) RACR knock-in; B2M Knock-out** 2) CAR Knock-in 3) Potency enhanced
iPSC Line	In-licensed GMP iPSC line
Editing Platform	CRISPR-based
Process	Feeder-free, serum free, xeno free



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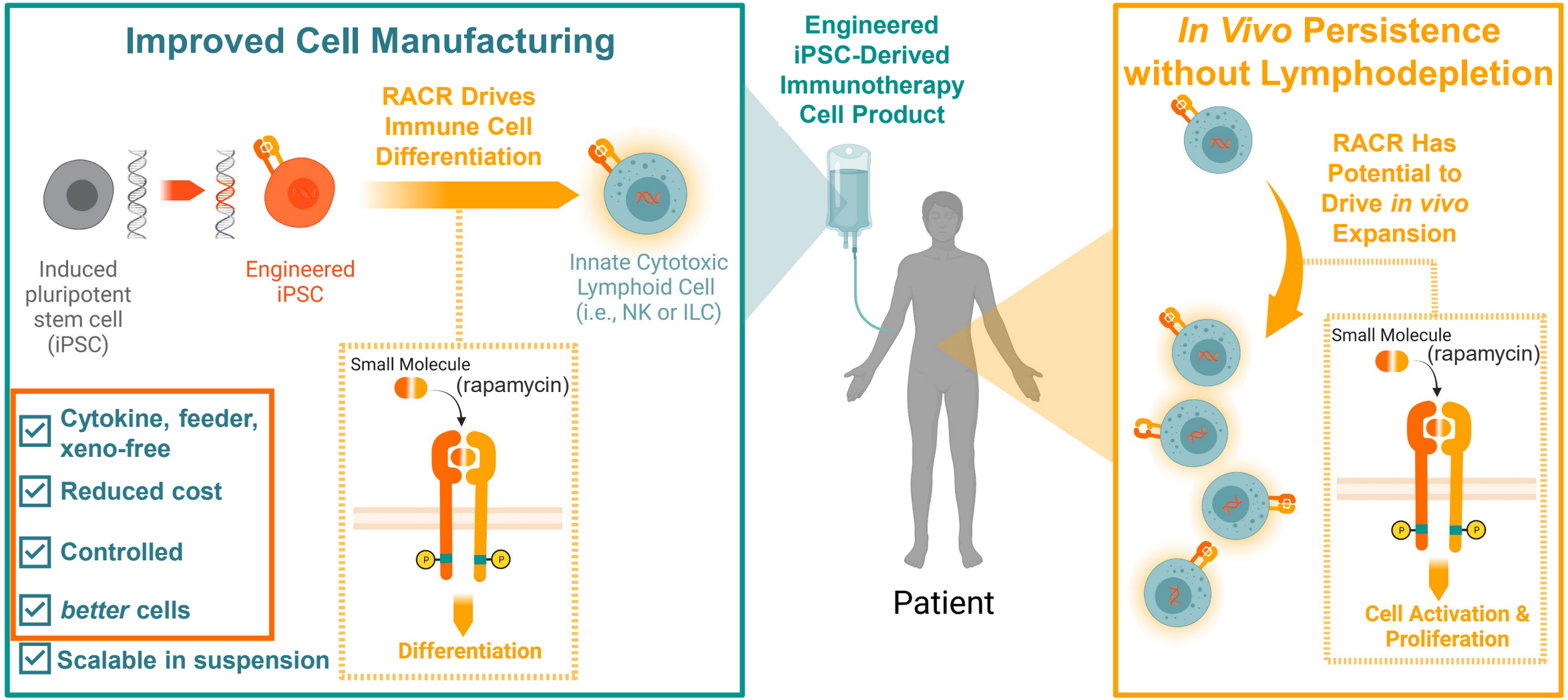
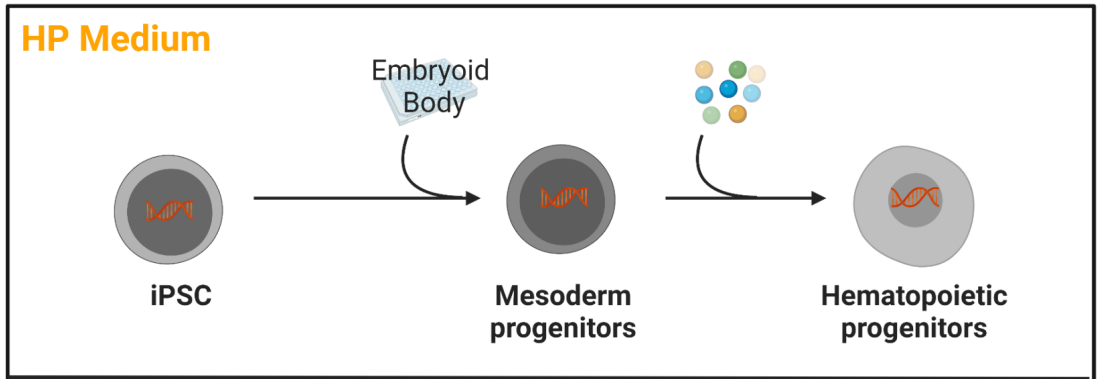
RACR: Engaging a Synthetic Cytokine Receptor for Cell Therapy Products

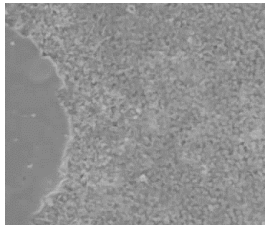


Using ShRED (Synthetic Receptor Enabled Differentiation) to Replace Growth Factor Addition and Minimize Variability of iPSC-HP Differentiation

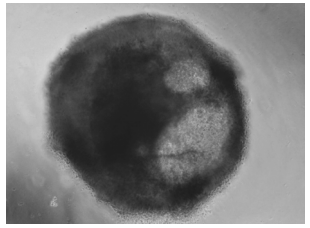
EXPAND

Traditional Process

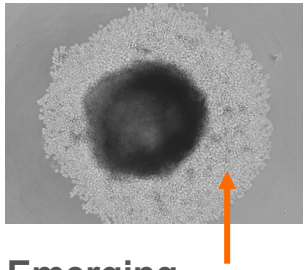




iPSCs

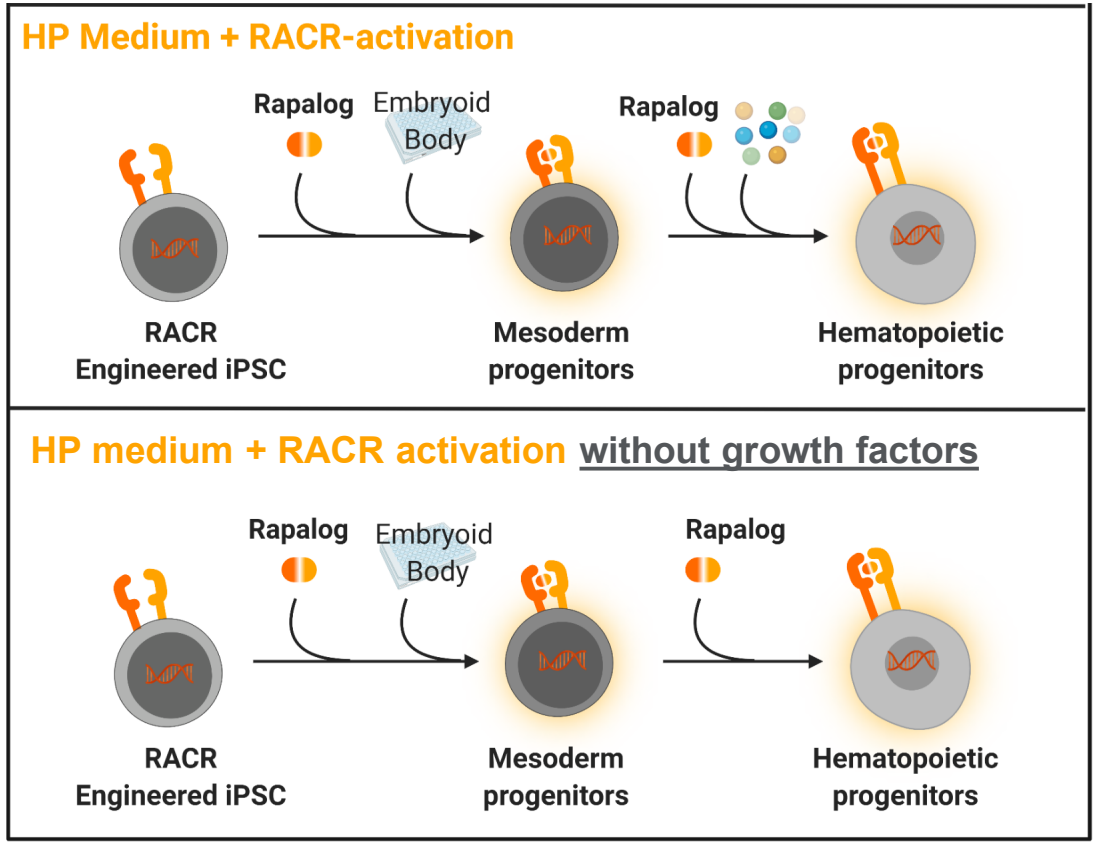


Embryoid Body (EB)



Emerging Hematopoietic Progenitor (HP) "Halo"

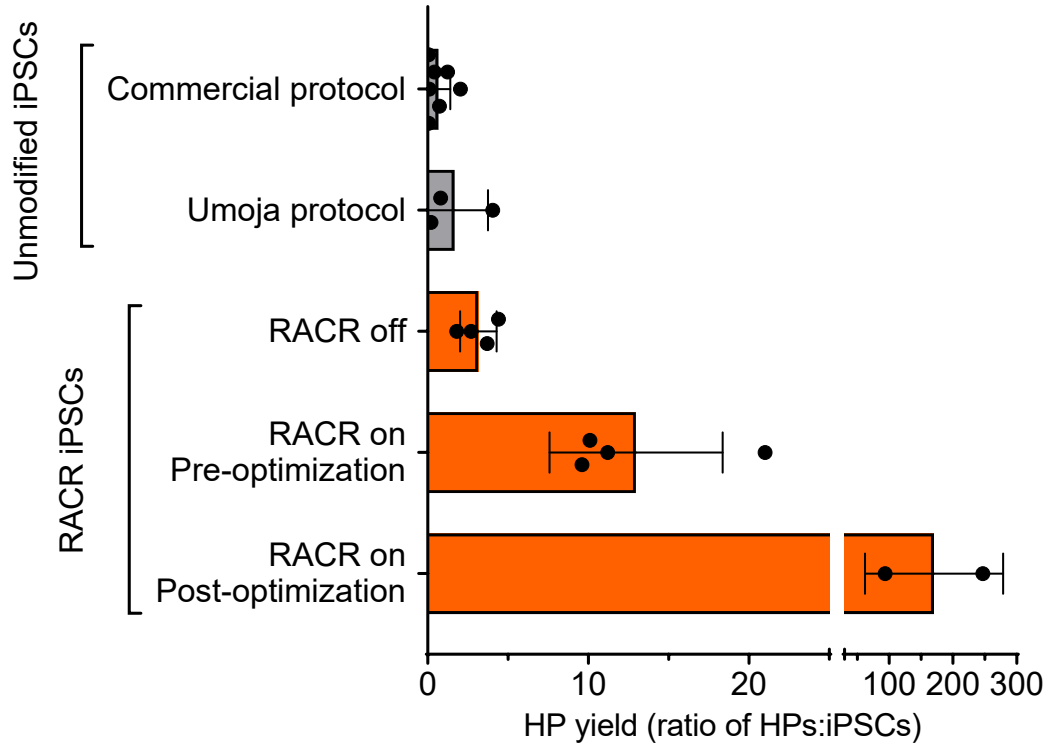
ShRED



ShRED enhances HP generation and yield <u>well beyond</u> any previous described approach

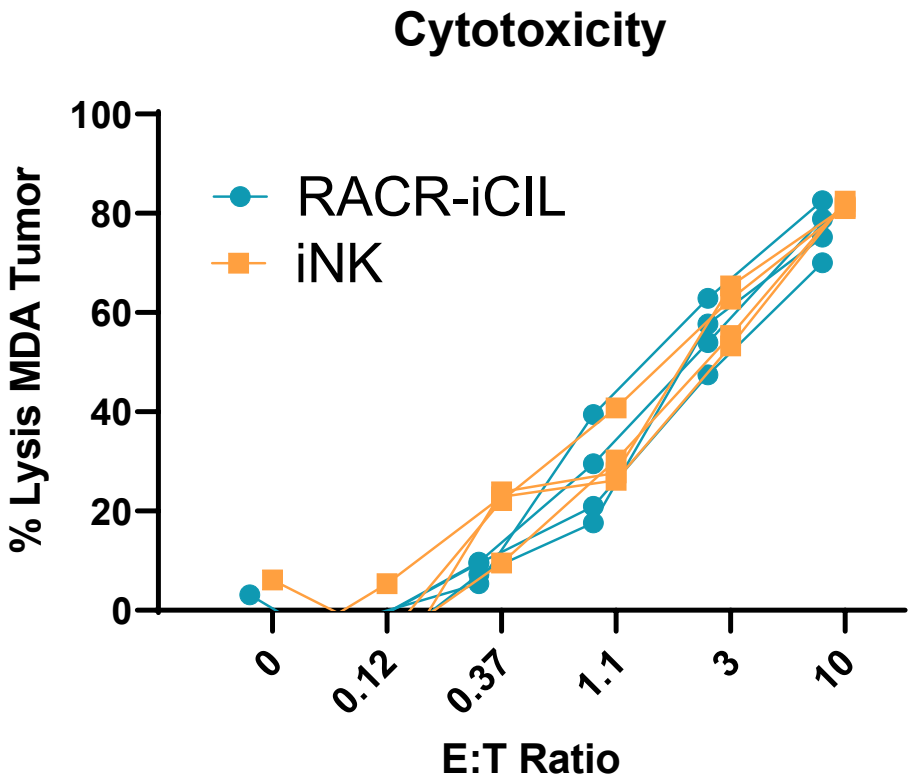
EXPAND

- When differentiating RACR-engineered iPSCs, RACR was activated via rapalog addition starting at day 0 of differentiation, and HP generation was measured at day 15
- Activating RACR during HP generation **increased HP yield >5x** compared to non-rapalog-treated controls in conventional cell culture format
- Improved culture conditions further enhanced RACR-driven HP yield (**≈125 HP:iPSC**)



Resultant iPSC-Derived Cytotoxic Innate Lymphocytes (iCILs) using RACR are Highly Functional & Cytotoxic

TARGET

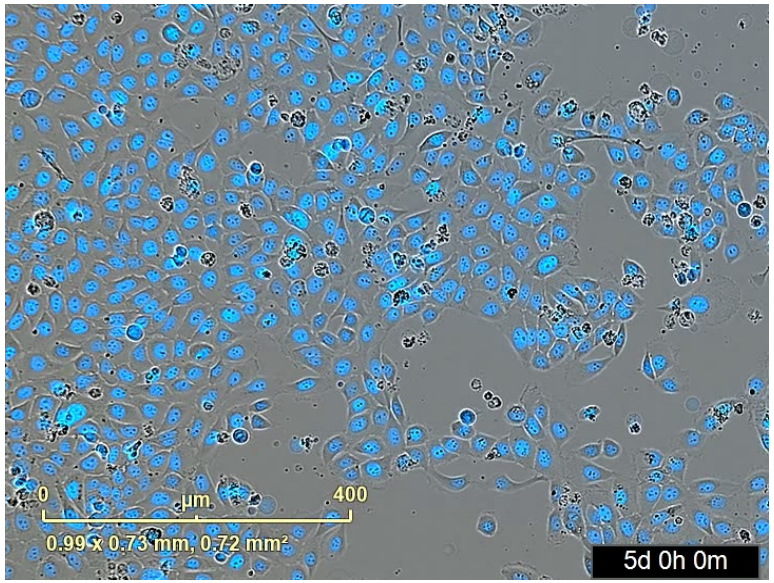


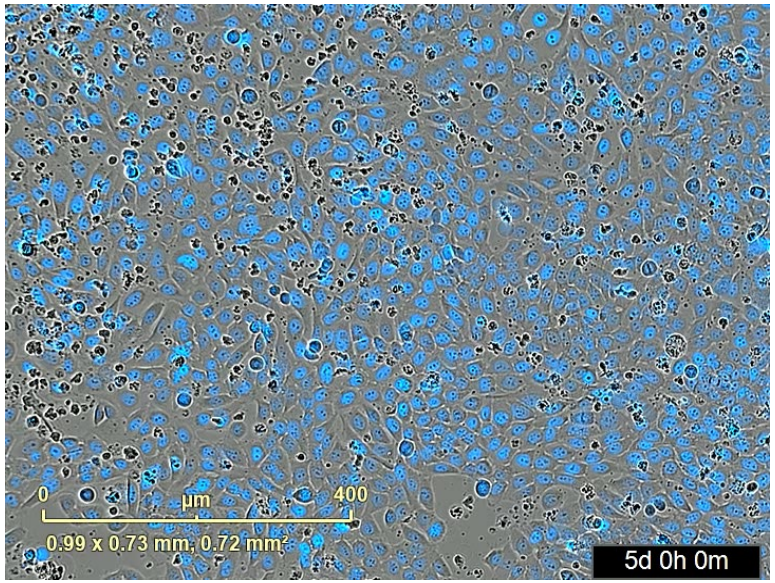
- **RACR-iCILs are highly functional & cytotoxic:**
  - Killing potency equivalent to NKs generated with standard differentiation protocols
  - May use RACR to avoid patient lymphodepletion, allowing for *in vivo* cytokine support of adoptively transferred iCILs

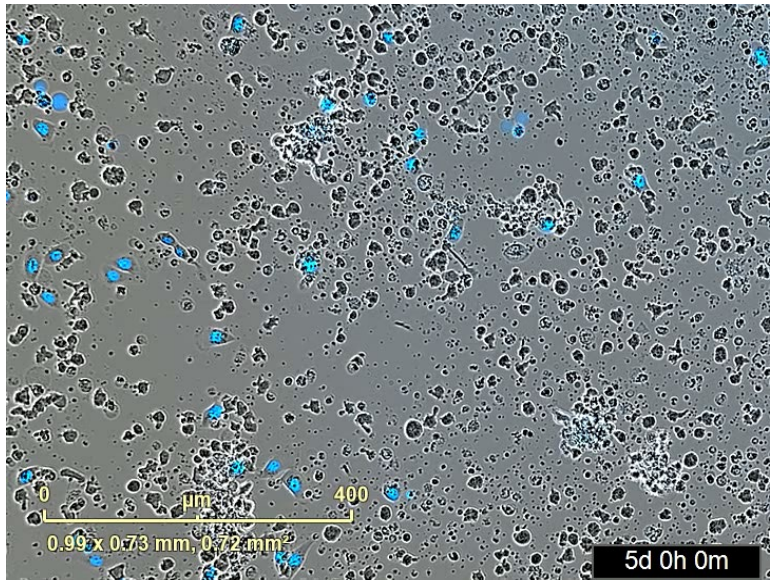
RACR-iCILs Display Improved Innate Cytotoxicity in Several Human Tumor Models

EXPAND

Tumor Only	Untreated NK cells	RACR-Stimulated NK cells (100nM Rapamycin)







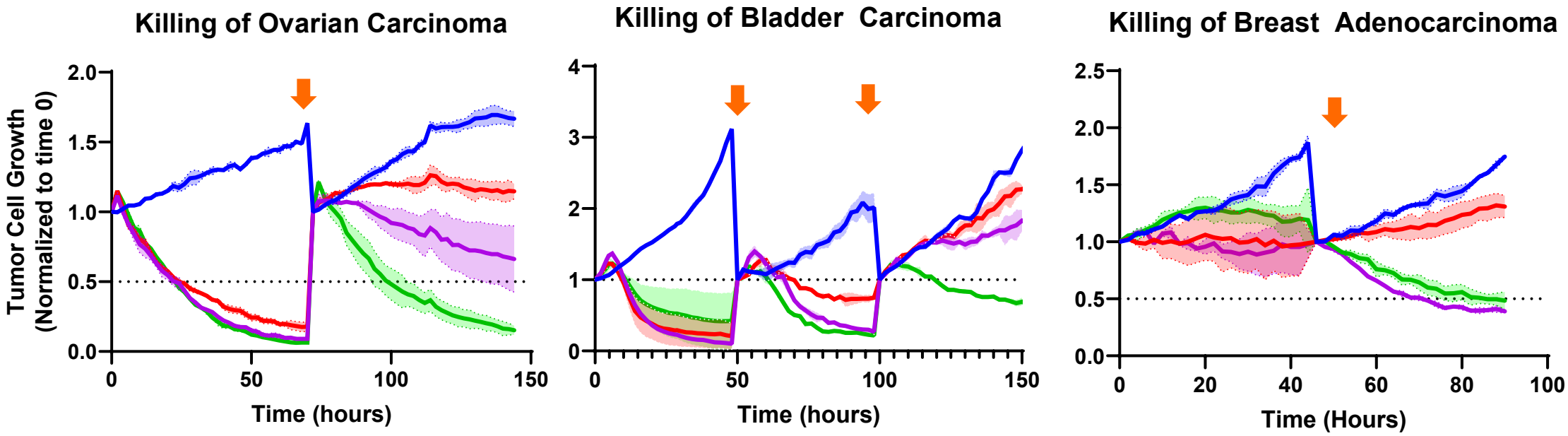
5637 Bladder Carcinoma cells

RACR-NK cells added at 10:1 effector to target ratio

Similar data has been generated in the Heme, Colon, Breast, Ovarian, and Uterine solid tumor lines.

RACR-iCILs Display Improved Innate Serial Killing in Several Human Tumor Models

EXPAND



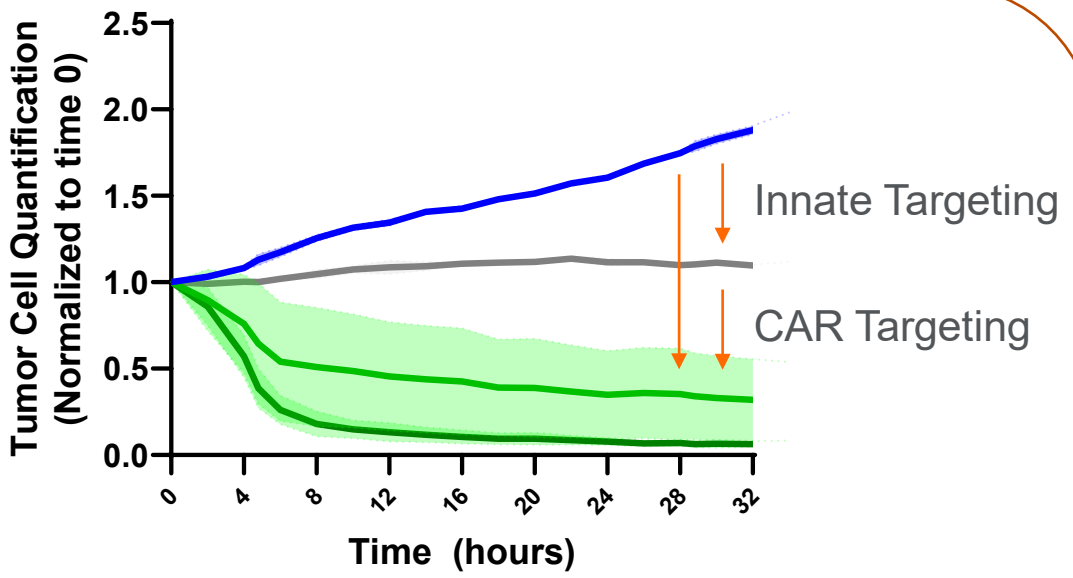
Tumor Only Control
10:1 RACR-Stimulated NK cells
10:1 Untreated NK cells
10:1 Cytokine-Stimulated NK cells

= Tumor cell re-challenge

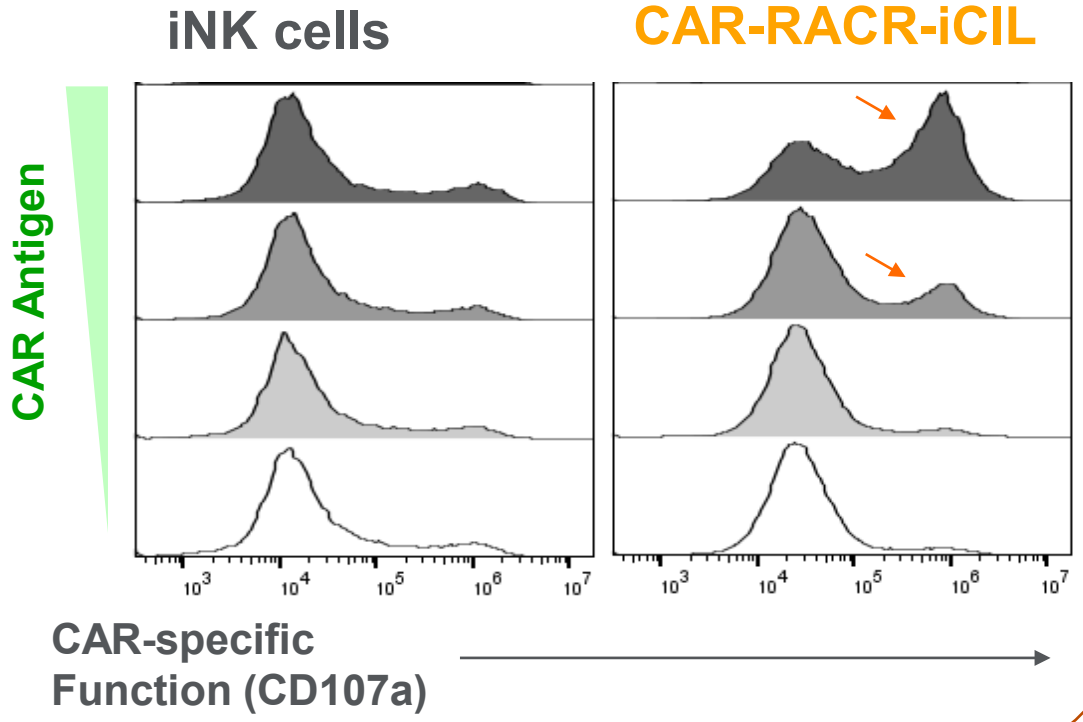
CAR-RACR-iCILs Display Potent and Specific CAR-Driven and Innate Tumor Killing

TARGET

Tumor Cell Killing



CAR-specific Function



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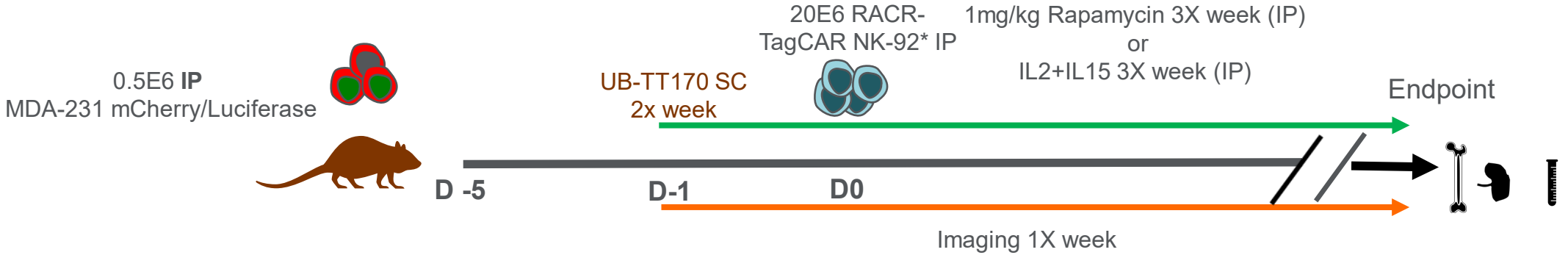
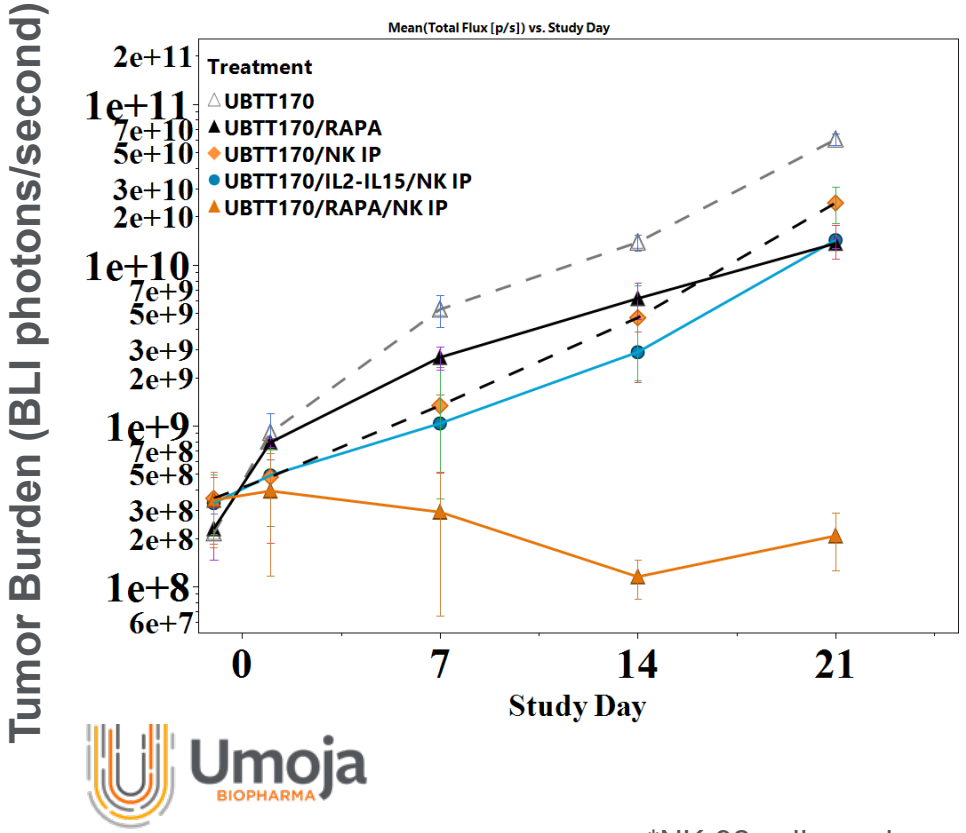
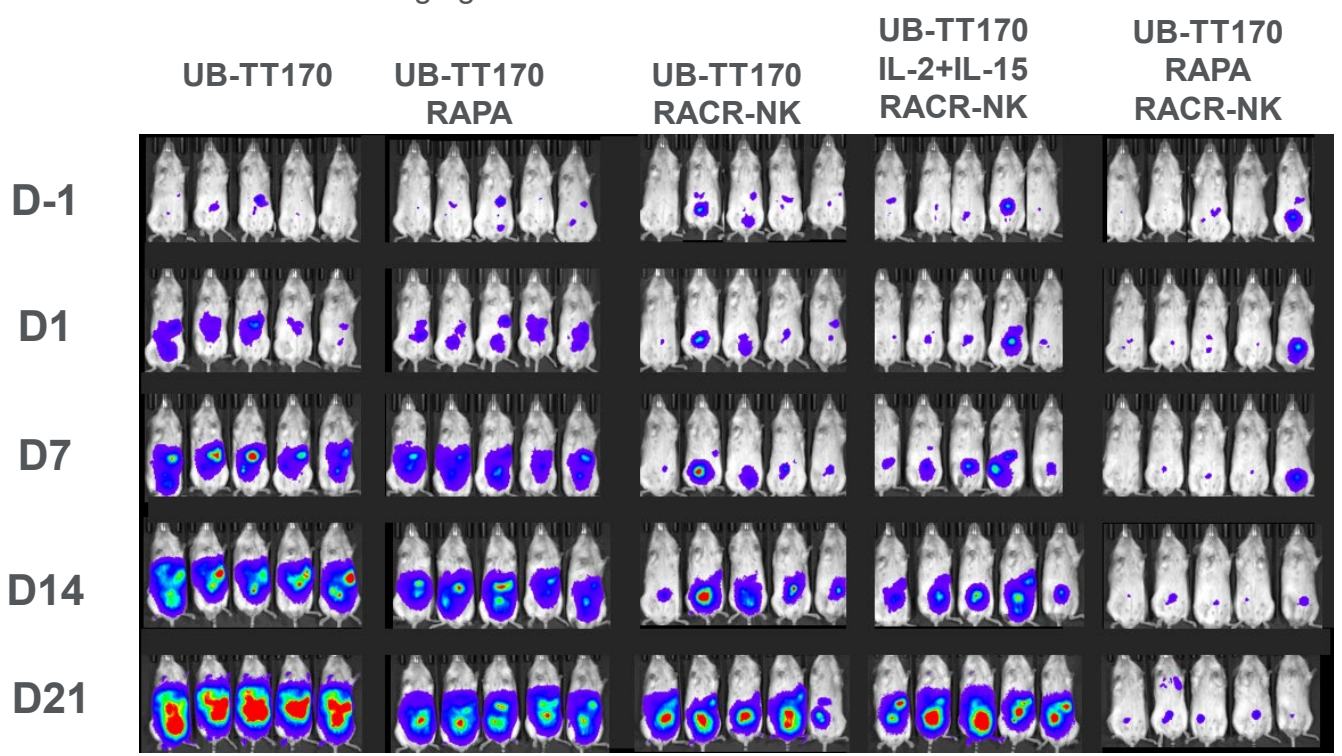
Engaging the RACR system in RACR-CAR engineered NK cells enhances tumor control in vivo

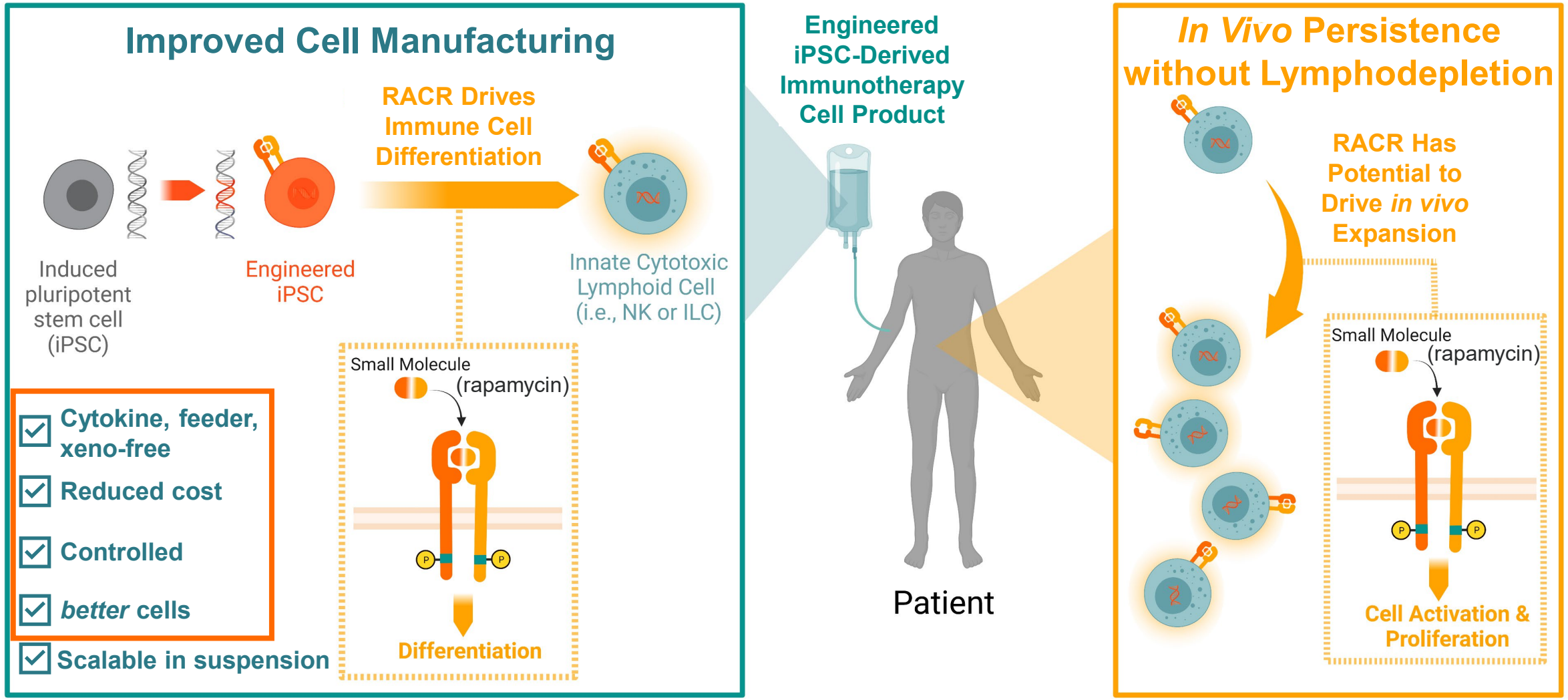






*NK-92 cells engineered with lentiviral vector to express RACR and TagCAR

RACR: Engaging a Synthetic Cytokine Receptor for Cell Therapy Products



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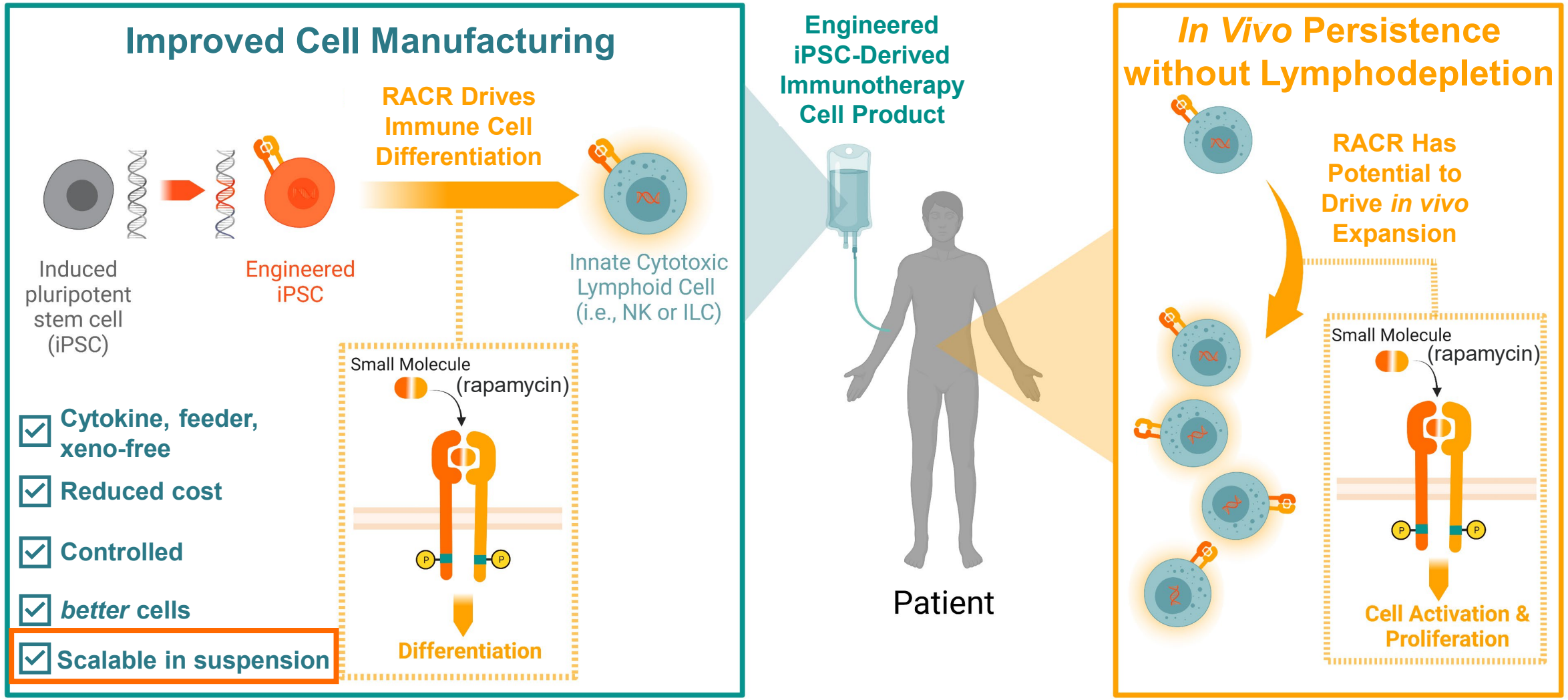
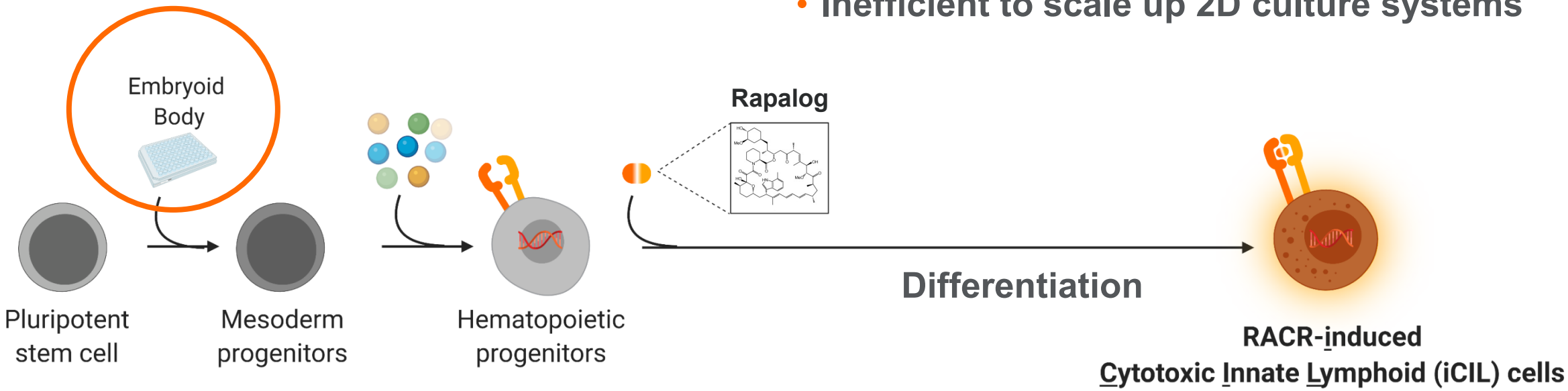


Scaling-Up Plate-Based Differentiation to a Suspension Culture System

EXPAND

- iPSCs prefer 2D culture (i.e., plates)
- Inefficient to scale up 2D culture systems



Pluripotent iPSC Aggregates in Suspension

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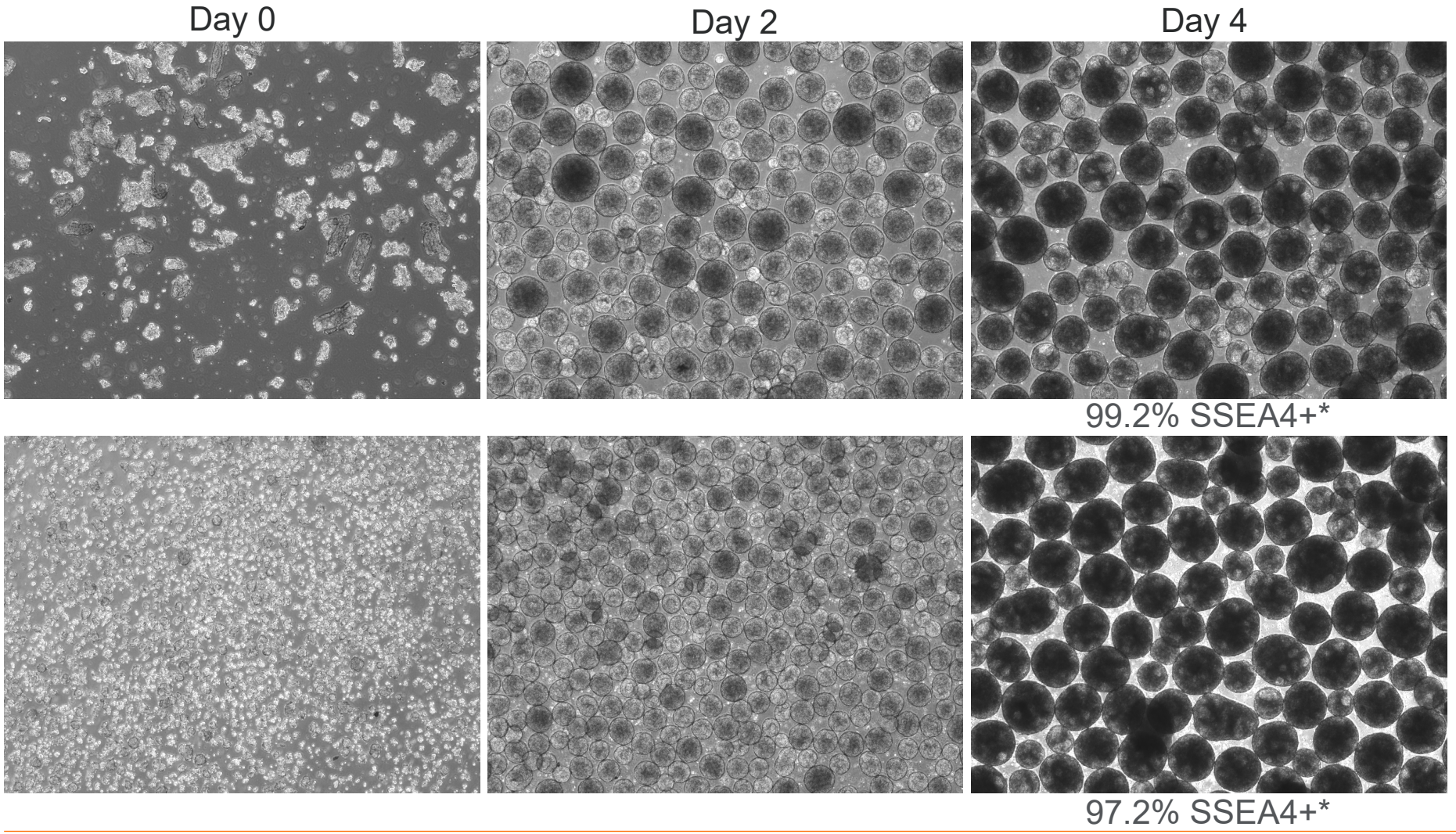

- Retain pluripotency marker expression after passaging in 3D (>97% SSEA4+)
- Yields iPSC concentrations of 1-2 x10^6 cells/mL

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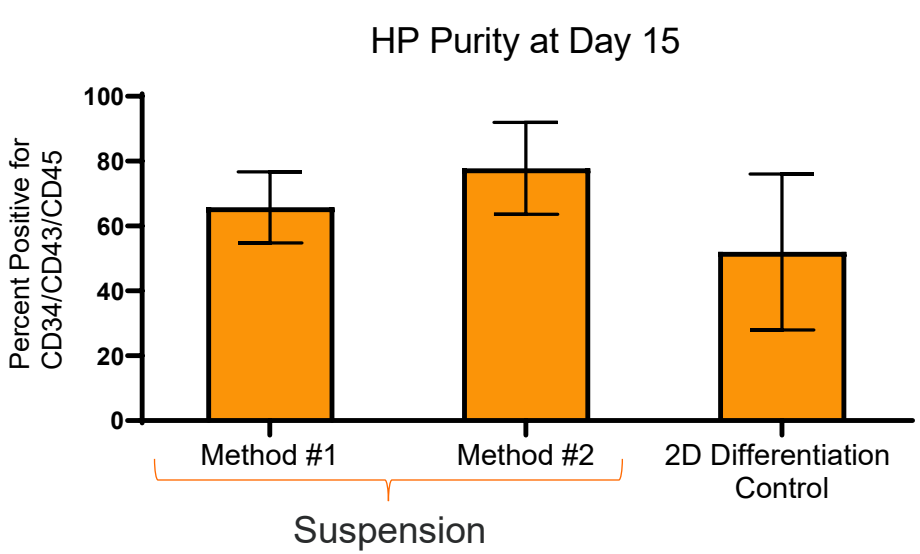
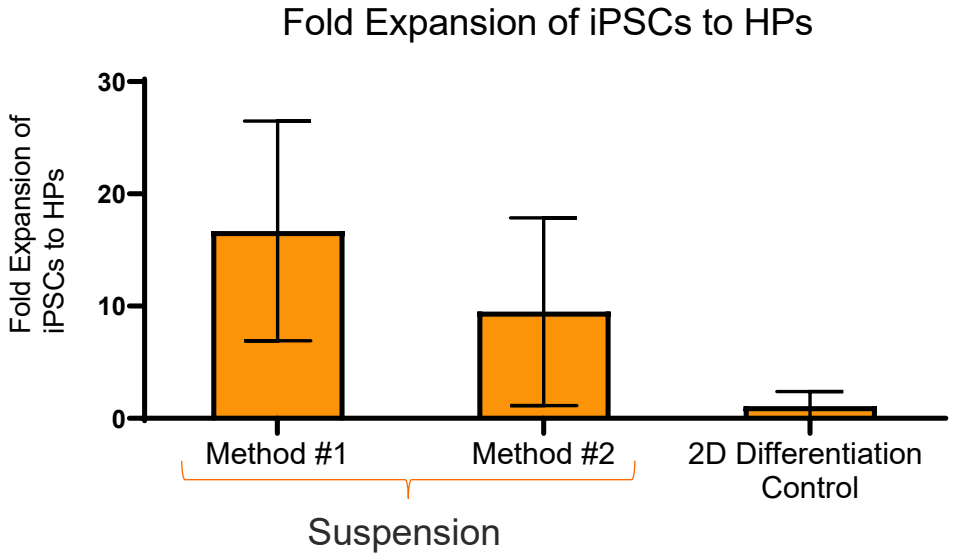
* SSEA4 is an iPSC marker indicative of pluripotency.

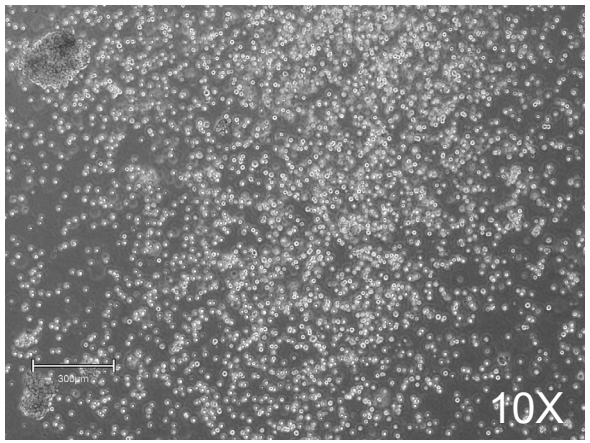
Hematopoietic Progenitors Generated in Suspension with High Yields

EXPAND





Harvested HPs



- **Reproducibly generate HPs in suspension**
  - Average 65-78% CD34+/CD43+/CD45+; Multiple protocols being adapted
- **Higher fold HP expansion than 2D control**
  - Yield of 9 to 17 HPs per iPSC, compared to 1 for 2D control
- **Good final concentration and viability**
  - Average 3x10^6 viable cells/mL harvested, 95% viable

Additional synergistic improvements anticipated when combined with ShRED

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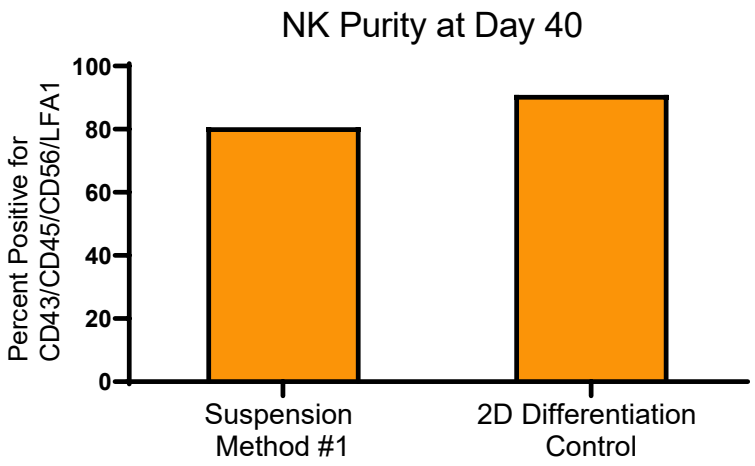
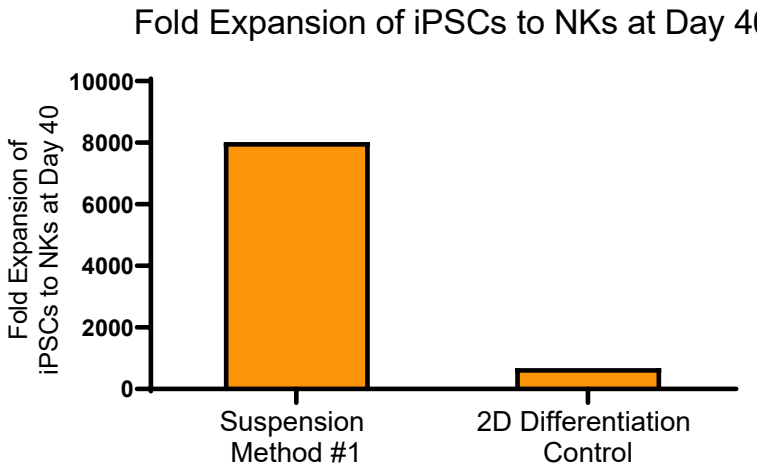
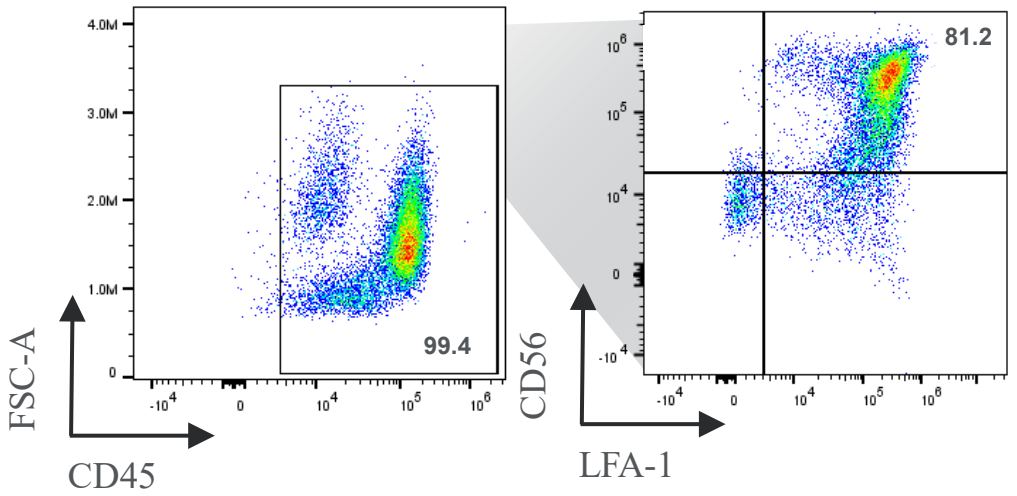
Generated iNKs Completely in Suspension with High Fold Expansion and High Purity

EXPAND







- **Generate high-purity iNKs in suspension**
  - >80% CD45+/CD56+/LFA+
- **Extremely high iNK fold expansion in suspension**
  - Yield of >8,000 iNKs per iPSC (from day 0 to 40)

Additional synergistic improvements anticipated when combined with ShRED

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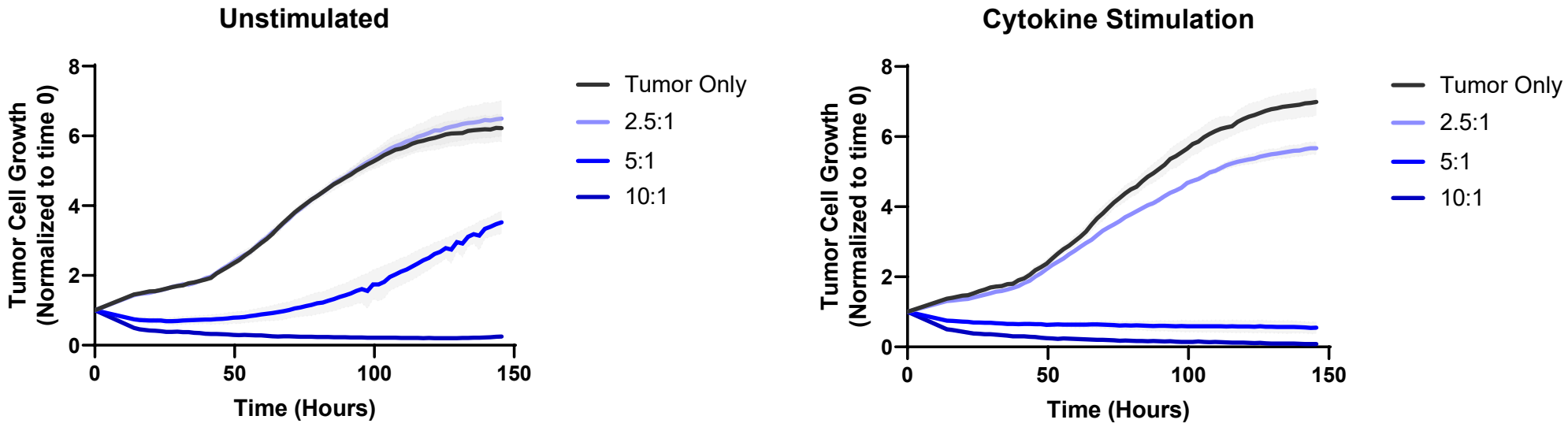
iNKs Generated in Suspension Display High Innate Cytotoxicity

EXPAND



- iNKs were exposed to breast adenocarcinoma cell line at different effector target ratios either in the presence or absence of cytokines (IL-2/IL-15).
- iNKs demonstrated robust clearance of tumor cells with faster clearance with cytokine support.

Umoja-TreeFrog Collaboration Highlights our Innovation and Leadership in Scalable iPS-Derived Immune Cell Manufacturing

ARM

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Your Body. Your Hope. Your Cure.

TreeFrog therapeutics

Umoja Biopharma and TreeFrog Therapeutics Announce Collaboration to Address Current Challenges Facing Ex Vivo Allogeneic Therapies in Immuno-Oncology

Partnership combines Umoja's technologies in gene-edited iPSCs and immune differentiation for persistent anti-tumor activity with TreeFrog Therapeutics' biomimetic platform for the mass-production of iPSC-derived cell therapies in large-scale bioreactors

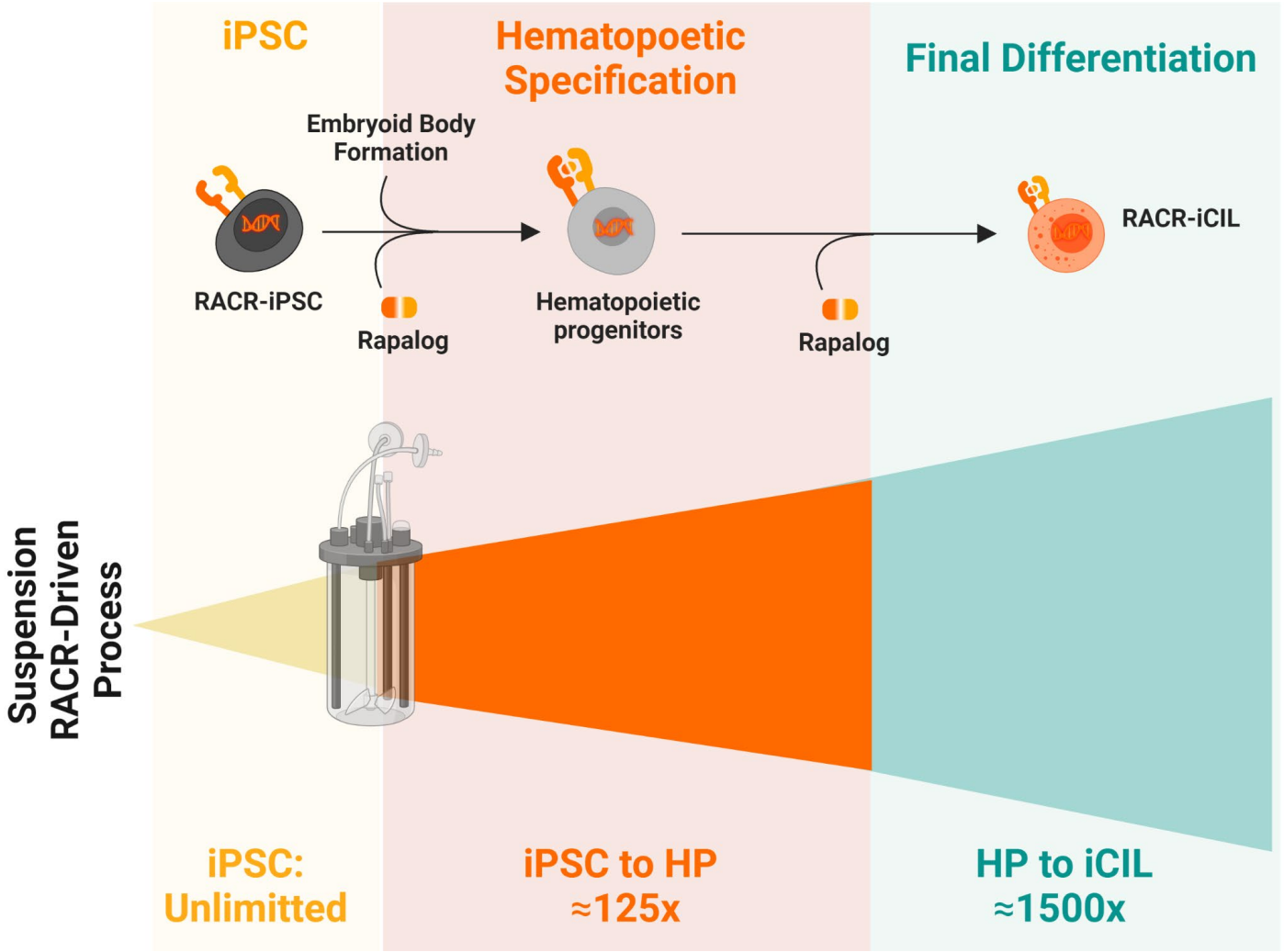
- Umoja thesis: scalable manufacturing is **essential** first step in iPS-derived cell therapies
  - Insufficient cells is at least partially at fault for lack of durable efficacy in current trials
- TreeFrog-enabled bioreactor driven ShRED to generate iCILs will drive COGs for a 1E10 iCIL dose below $500

Hurdles that Umoja Biopharma is Overcoming in Today's Cancer Immunotherapy Space

Today's Challenges	Umoja's Solutions
• Today's cell therapies are **too expensive**, even despite patient assistance programs	• Umoja's iPSC-derived approach **removes the vast majority** of manufacturing costs
• Today's oncology treatment—including cell therapies—are often **highly toxic** for patients to receive	• Umoja's approach **removes cytotoxic steps** like chemotherapy while preserving patient-specificity in treatment
• Today's cell therapies are only offered in a **small number of hospitals**	• Umoja's platform is expected to bring treatment to a **broader range of healthcare institutions**
• Today's cell therapies require **lengthy hospital stays** away from home	• Umoja's iPSC-derived approach is expected to be **a primarily outpatient experience**
• Today's ex vivo manufacturing approach is **unreliable and oftentimes ineffective**	• Umoja's platform generates **synthetic cells** which we expect to yield a more reliable product
• Patients **cannot survive** the manufacturing period of today's cell therapies	• Umoja's iPSC-approach generates cells "**off-the-shelf**", without any lengthy manufacturing wait

Vision: Umoja Biopharma's RACR-driven ShRED Aims to Address Multiple iPSC-Derived Immune Cell Manufacturing Challenges

EXPAND



1. **Engaging RACR** for improved HP differentiation
2. **Fully scalable, suspension-based** differentiation process
3. **Serum-free, feeder-free, xeno-free**

Our system aims to avoid the use of plates and exhaustive feeder expansions by providing a fully-scalable, xenogeneic-free, RACR-driven iCIL CMC process

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Thank You

Questions?

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