



Programmed Cellular Immunotherapies

Overview of Universal, Off-the-Shelf Cancer Immunotherapy Programs

June 6, 2019

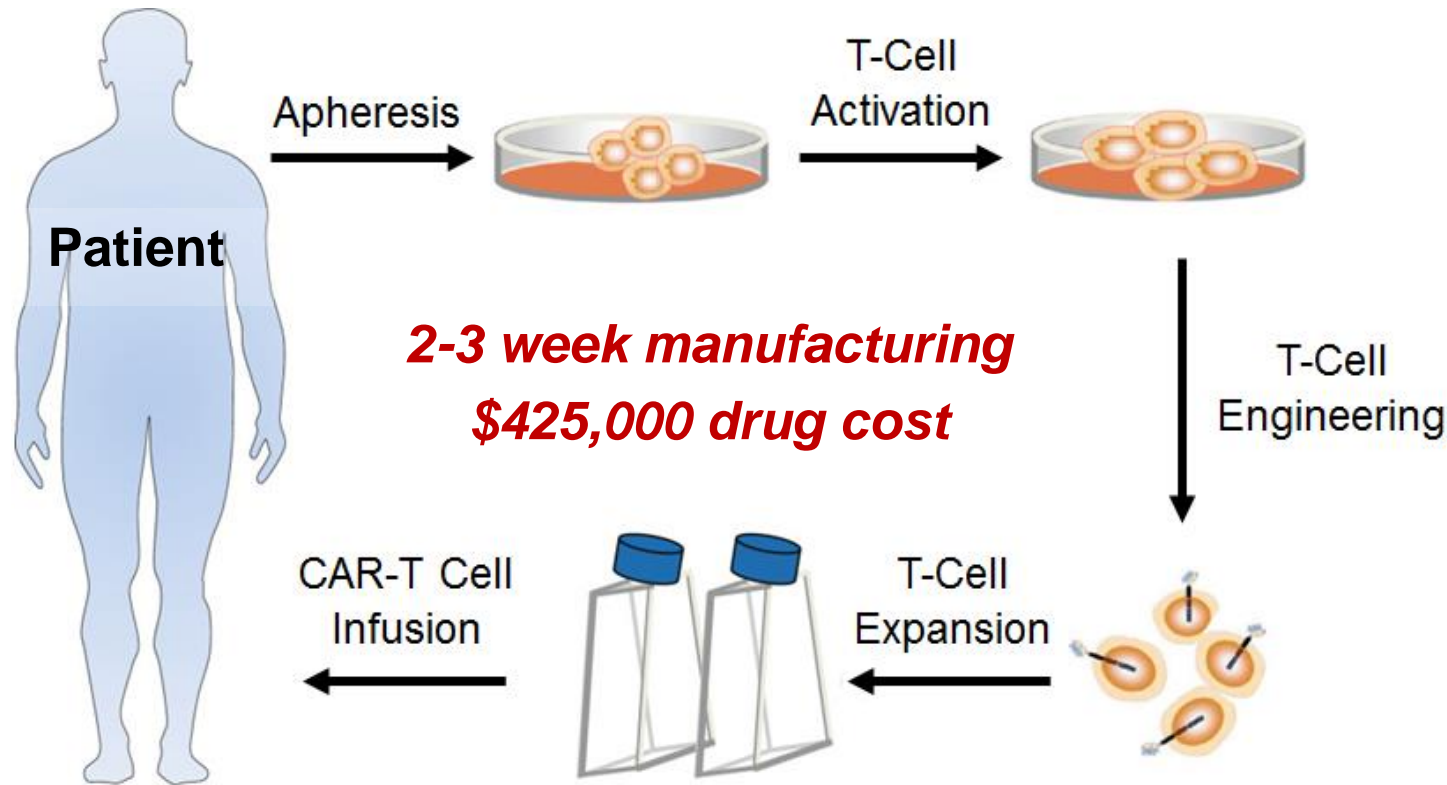
Forward-Looking Statements



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First Innings of Cell Therapy Development

Patient-derived CAR-T Cell Immunotherapy



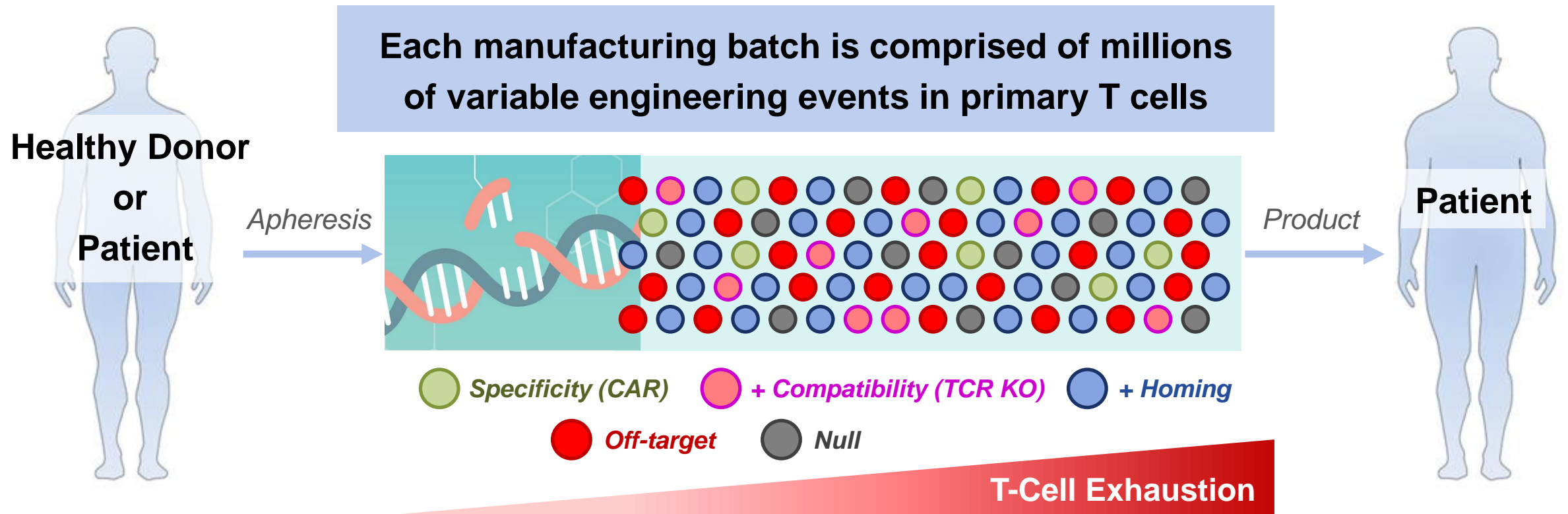
"When factoring in all the costs associated with CAR T-cell therapy, hospitals may charge as much as \$1.5 million or more to avoid losing money."

Richard T. Maziarz, MD
Professor of Medicine, Oregon Health & Science University's Knight Cancer Institute

Impaired Starting Material | **Random & Variable** Engineering | **Complex** Logistics
Heterogeneous Drug Product | **Expensive** | **Single-dose** Limitation

First Innings of Cell Therapy Development

Batch-to-Batch Engineering is Expensive and Results in Significant Product Heterogeneity



How do we build on early successes and transition from a heterogenous process to the cost-effective delivery of optimized cell products?

Changing the Game in Cell-based Cancer Immunotherapy

The Potential to Select, Characterize and Renewably Use a Single Cell



What if we had the opportunity to renewably use a single cell?

Changing the Game in Cell-based Cancer Immunotherapy

Universal, Off-the-Shelf Cell Products Derived from Renewable Master Cell Lines



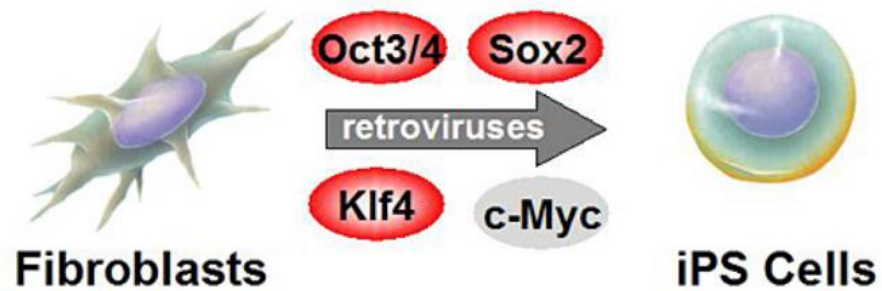
Key Features	Cell Therapy 1.0 and 2.0	Cell Therapy 3.0
Cell Source	Patient and Donor Cells	Renewable Master Cell Line
Genetic Engineering	Random & Variable	Uniform & Complete
Characterization	Imprecise	Well-defined
Product Identity	Heterogeneous	Homogeneous
Manufacturing	Limited Dose Availability	Off-the-Shelf Availability
Cost-per-Dose	High	Low
Dosing	Single Dose	Multiple Doses / Multiple Cycles
Overall Paradigm	Process-centric	Product-centric

Human Induced Pluripotent Stem Cells (iPSCs)

Reprogramming Adult Somatic Cells to a Pluripotent State



Generation of Human iPSCs



Mouse iPS cells reported in 2006
Human iPS cells reported in 2007

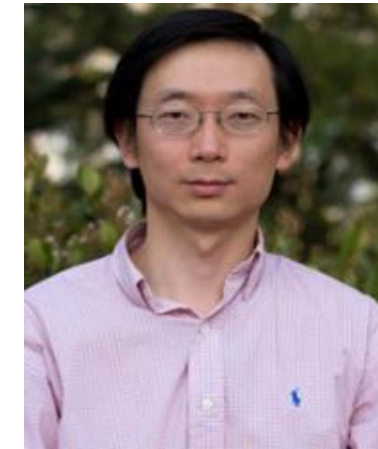
Fate Scientific Founders



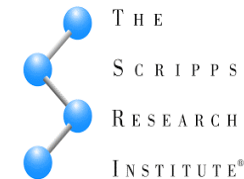
Rudolf Jaenisch, MD



WHITEHEAD INSTITUTE



Sheng Ding, PhD



THE
SCRIPPS
RESEARCH
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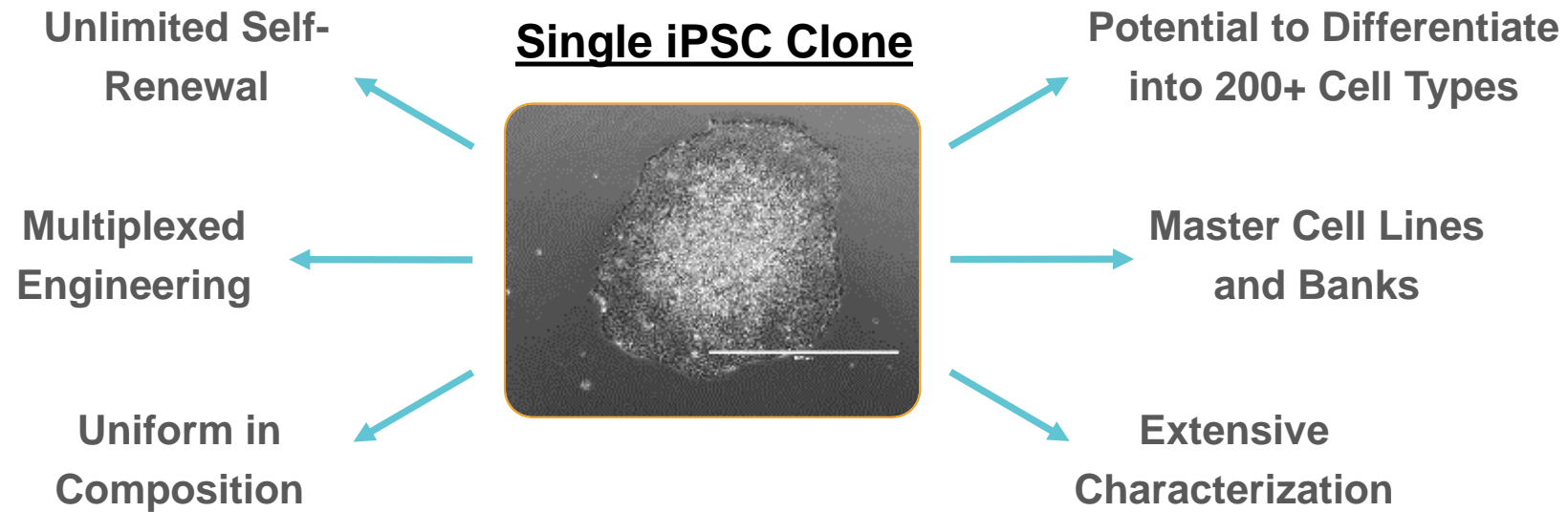
Unique Advantages of Human iPSCs

Isolation, Characterization & Selection of a Single iPSC Clone



A Single Human Induced Pluripotent Stem Cell (iPSC)

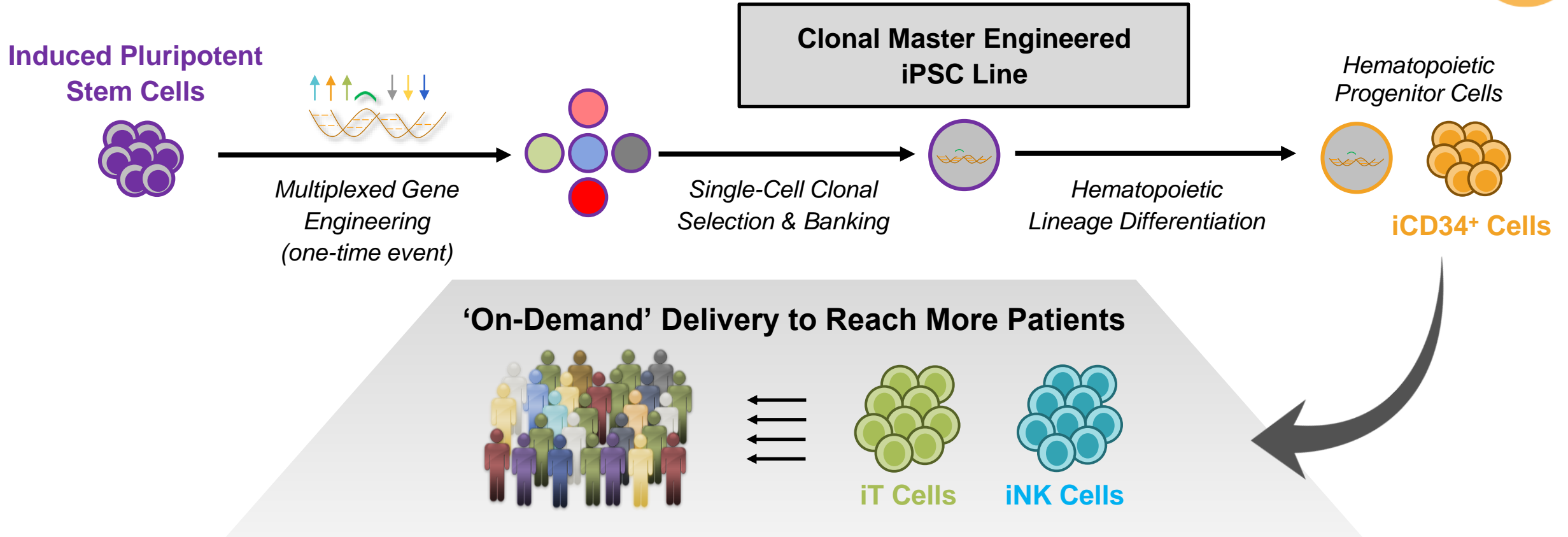
A renewable source for making cells



Fate Therapeutics' iPSC product platform is supported by an IP portfolio of 100+ issued patents and 100+ pending patent applications

Off-the-Shelf Cell-based Cancer Immunotherapy

iPSC Product Platform for Mass Production of Universal NK Cell and T-Cell Products



Clonal master iPSC lines are a renewable cell source that can be repeatedly used to mass-produce homogeneous, cryopreserved cell product in a cost-effective manner

Off-the-Shelf Cell-based Cancer Immunotherapy

Systematic Build of Industry-Leading iPSC-derived NK Cell Product Pipeline

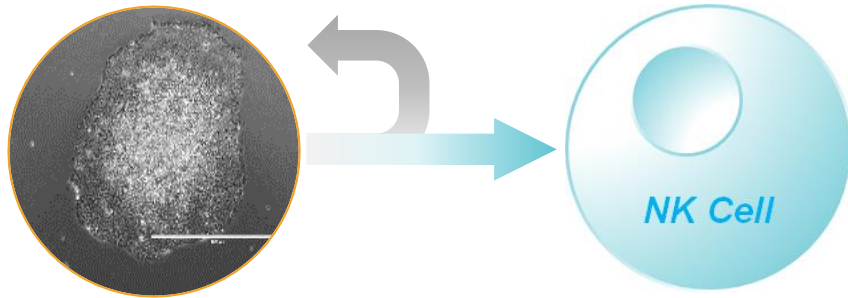


Universal, Off-the-Shelf NK Cell Cancer Immunotherapy Pipeline

Clonal Master iPSC Line	Synthetic Biology	FT500	FT516	FT596	FT538	FT576
Multi-faceted Innate Immunity		✓	✓	✓	✓	✓
+ High-Affinity, Non-cleavable 158V CD16	<i>Augment mAb therapy</i>		✓	✓	✓	✓
+ IL-15 Receptor Fusion	<i>Enhance NK cell function</i>			✓	✓	✓
+ CAR Insertion	<i>Target tumor-associated antigen</i>			CD19		BCMA
+ CD38 Knock-out	<i>Resist CD38-mediated fratricide</i>				✓	✓
	Total # of Synthetic Elements	0	1	3	3	4

FT500 Universal, Off-the-Shelf NK Cell Product Candidate

Multi-faceted Innate Immune Function



Master iPSC Line

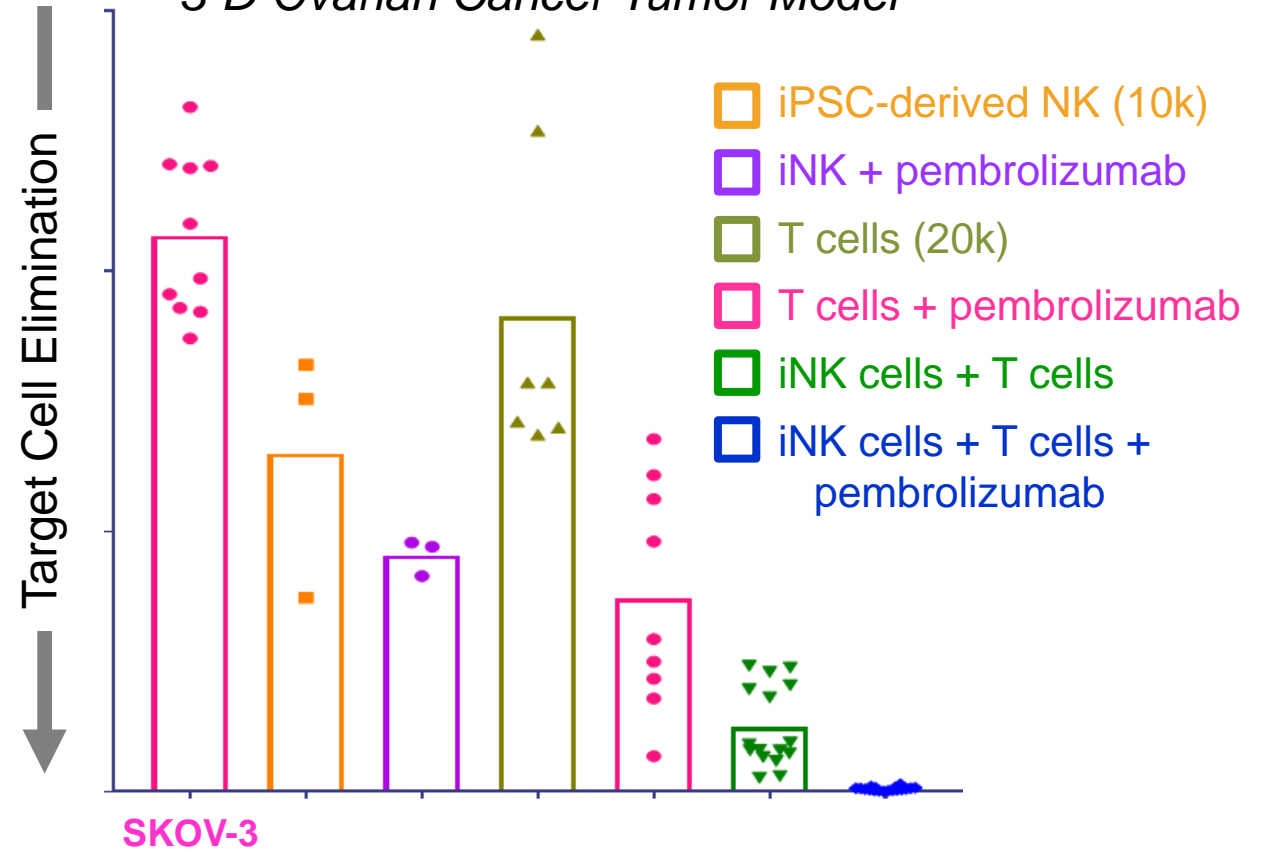
FT500

- High levels of expression of potent activating receptors (NKG2D, NKp30/40/46)
- High levels of secretion of cytolytic proteins (perforin and granzyme B)
- Low levels of expression of checkpoint receptors (PD-1, LAG-3 and TIGIT)

Target cell recognition via stress ligands and non-self MHC-I expression

Bridging Innate and Adaptive Immunity

3-D Ovarian Cancer Tumor Model



FT500 Universal, Off-the-Shelf NK Cell Product Candidate

100s of Cryopreserved Doses in Single GMP Campaign from Master iPSC Line



Low-cost per Dose GMP Production of Homogeneous Cell Product

GMP Manufacturing Site

Molecular and Cellular Therapeutics
University of Minnesota



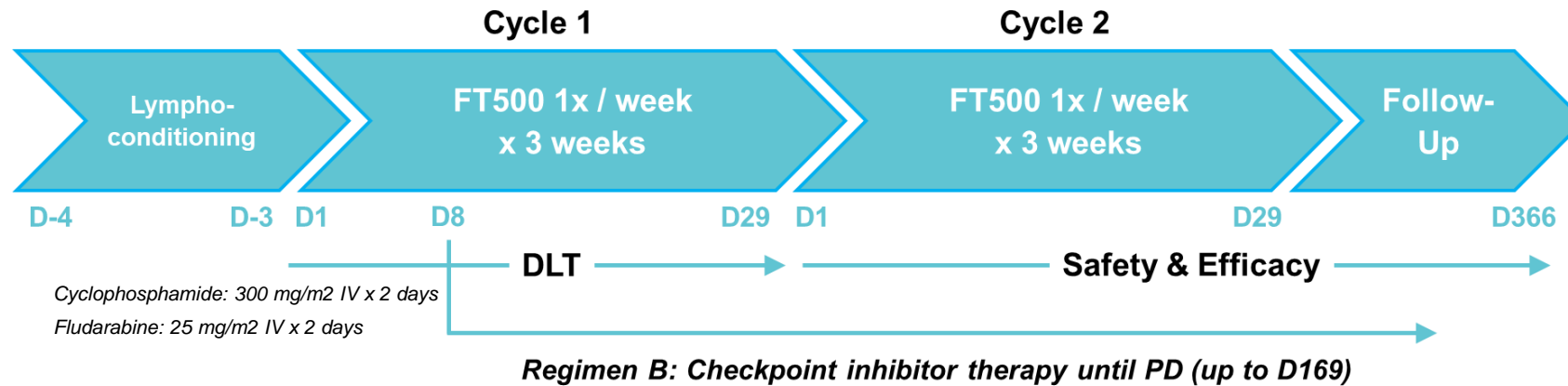
FT500 Cell Product		
Identity, CD45+	100%	
Identity, CD45+CD56+	98%	
Viability	80%	
Residual iPSCs	Not detected	
Packaging	Cryopreserved	
Storage	Clinical sites	
Administration	Thaw-and-infuse 'on demand'	
Delivery	Outpatient setting	

FT500 Universal, Off-the-Shelf NK Cell Product Candidate

Phase 1 Study Design: Multiple Doses over Multiple Cycles for Advanced Solid Tumors



First-ever Clinical Trial in U.S. of iPSC-derived Cell Therapy



Regimen A – Monotherapy*

- Salvage therapy for advanced solid tumors
- Dose Escalation: 100M and 300M cells per dose
- Dose Expansion: up to 10 subjects

Regimen B – Checkpoint Inhibitor (CPI) Combination*

- Progressed or failed CPI for advanced solid tumors
- Dose Escalation: 100M and 300M cells per dose + CPI
- Dose Expansion: up to 30 subjects

KEYTRUDA
(pembrolizumab) Injection 100 mg

OPDIVO
(nivolumab)

TECENTRIQ
atezolizumab

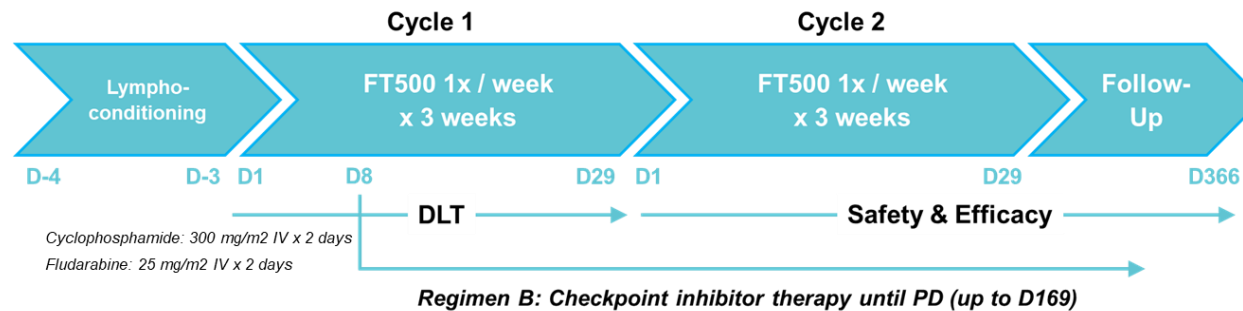
*If a CR, PR or SD \geq 24 weeks is observed, up to 10 subjects with that specific tumor type may be added to Dose Expansion

FT500 Universal, Off-the-Shelf NK Cell Product Candidate

Phase 1 Study Design: Multiple Doses over Multiple Cycles for Advanced Solid Tumors



First-ever Clinical Trial in U.S. of iPSC-derived Cell Therapy



Regimen A – Monotherapy

- DL1 = 100M cells per dose (n=3)
 - All 3 subjects received 6 doses
 - No reported DLTs
- DL2 = 300M cells per dose
 - Subjects treated

Regimen B – Checkpoint Inhibitor (CPI) Combination

- DL1 = 100M cells per dose
 - Subjects treated

FT500 Patient Enrichment Strategy in CPI Resistant Patients

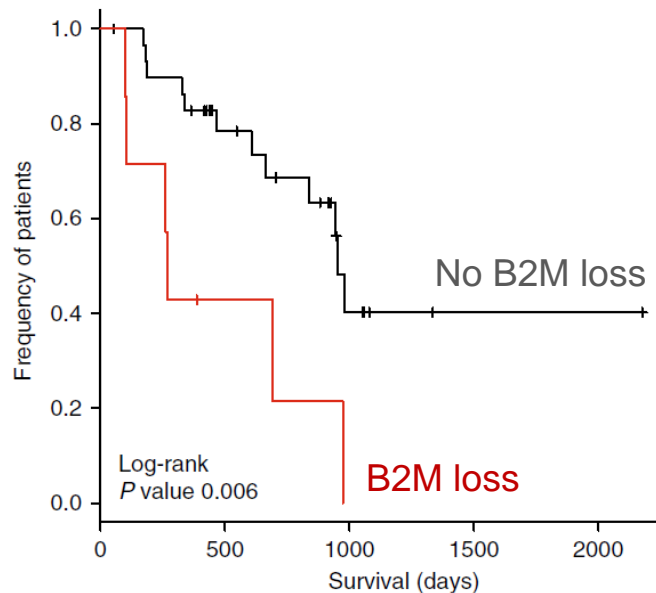
Regimen B: Rescue Therapy for Patients with Loss-of-Function Mutations



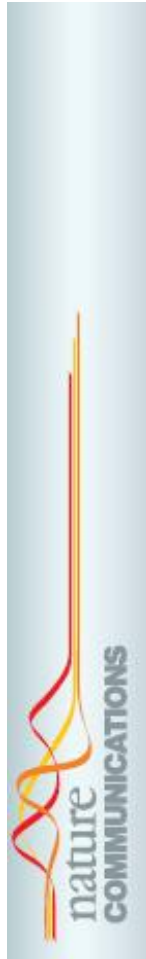
DOI: 10.1038/s41467-017-01062-w

Resistance to checkpoint blockade therapy through inactivation of antigen presentation

Survival



- ✓ MHC Class I expression on tumor cells is required for detection and destruction by T cells
- ✓ Loss or down-regulation of MHC Class I is a major tumor escape mechanism in solid tumors
- ✓ MHC Class I null tumor cells are highly susceptible to killing by NK cells
- ✓ Several tumor cell mutations, including in B2M gene, disrupt MHC Class 1 expression
- ✓ B2M mutations are enriched in patients who are resistant to checkpoint blockage (~30%) and are associated with poor survival



FT500 Universal, Off-the-Shelf NK Cell Product Candidate

Phase 1 Study: Key Objectives



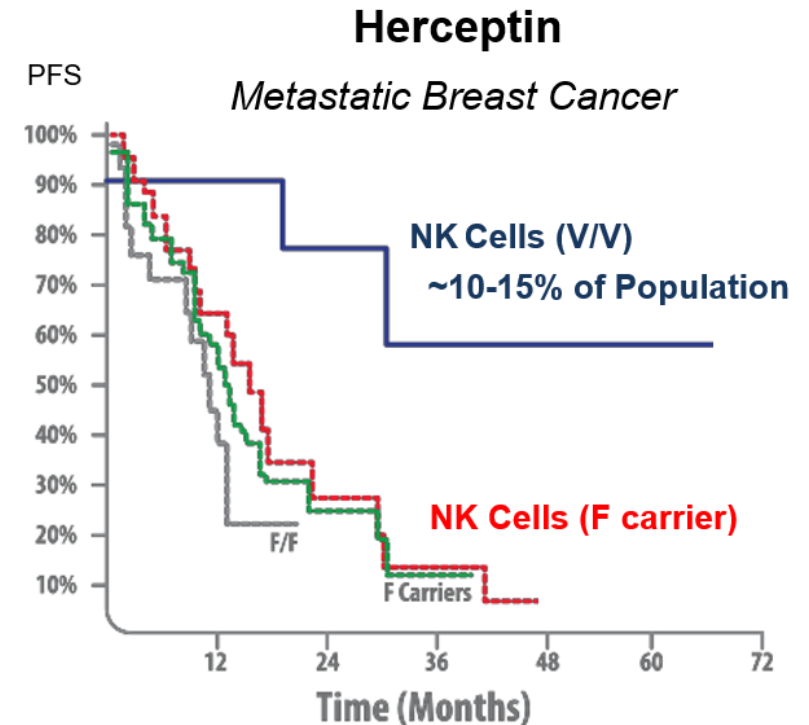
Proprietary Learnings Accruing to our iPSC-derived Product Pipeline

- **Safety**
 - First-ever iPSC-derived cell therapy to undergo clinical investigation in U.S.
 - Regimen B includes novel combination of iPSC-derived NK cell with checkpoint inhibitor therapy
- **Tolerability**
 - Off-the-shelf, cryopreserved, thaw-and-infuse (unmatched) cell product
 - Multiple doses over multiple cycles (3 doses per cycle; 2 cycles) administered in outpatient setting
- **Biomarkers**
 - Dose durability, including variance over dosing schedule
 - Anti-cell immunogenicity
 - FT500 infiltration of tumor / tumor remodeling
 - Endogenous T-cell and cytokine response
- **Patient Conditioning**
 - Lympho-conditioning regimen
 - Cytokine support

FT516 NK Cell Expression of Naturally-Occurring CD16

Fc Receptor Mediates Antibody-Dependent Cellular Cytotoxicity (ADCC)

- CD16 mediates antibody-dependent cellular cytotoxicity (ADCC), a potent anti-tumor mechanism by which NK cells recognize, bind and kill antibody-coated cancer cells
- CD16 occurs in two variants: high (158V) or low (158F) affinity for the Fc domain of IgG1 antibodies
 - Only ~15% of patients are homozygous for 158V
 - Numerous clinical studies with FDA-approved tumor-targeting antibodies, including rituximab, trastuzumab and cetuximab, have demonstrated that patients homozygous for 158V have improved clinical outcomes
- CD16 has been shown to undergo considerable down-regulation in cancer patients and shedding in the tumor microenvironment, which can significantly limit endogenous NK cell activity and inhibit anti-tumor activity

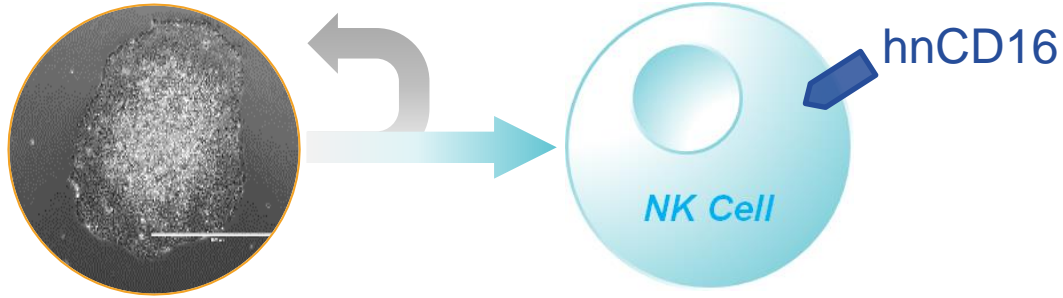


Musolino et al, *J. Clin Oncol*, 26, 1789, 2008

How to bring the 158V CD16 NK cell experience to all patients?

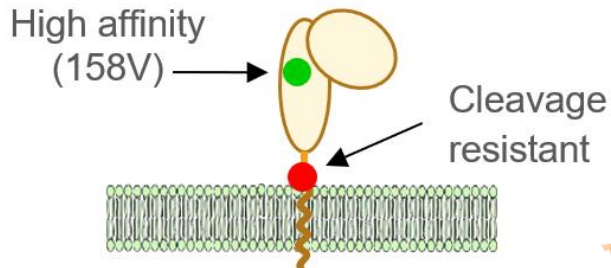
FT516 Universal, Off-the-Shelf hnCD16 NK Cell Product Candidate

High-Affinity 158V Engagement with Monoclonal Antibody for Enhanced ADCC



Engineered Master iPSC Line

FT516 + mAb



Modified form of CD16a
IgG antibody-binding receptor
resists shedding upon activation

Rituxan
Rituximab

DARZALEX
(daratumumab)

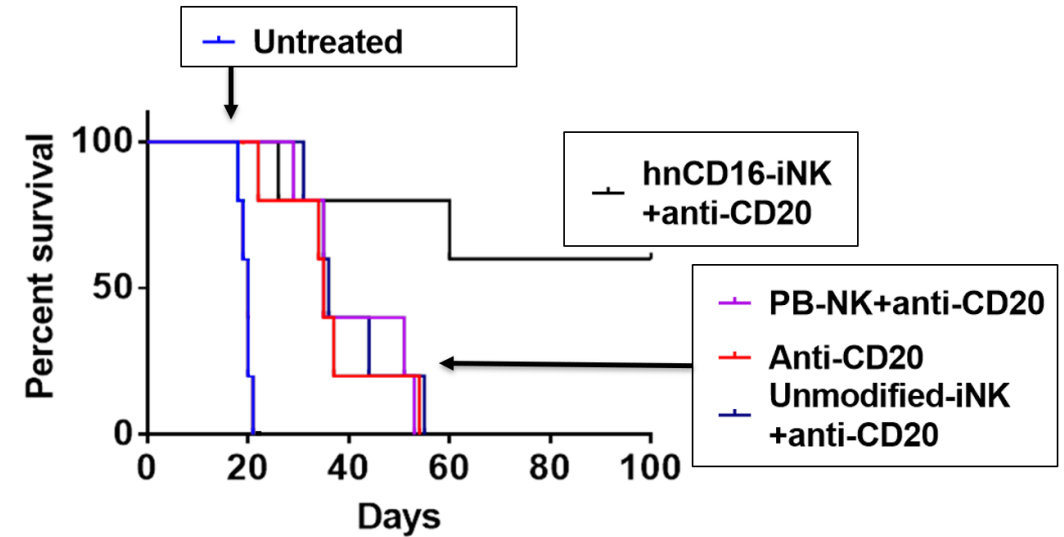
Herceptin
trastuzumab
Precision • Power • Promise

ERBITUX
Cetuximab

AVASTIN
bevacizumab

Enhanced Survival *In Vivo* with Rituximab

Mouse model of human lymphoma (Raji cells)



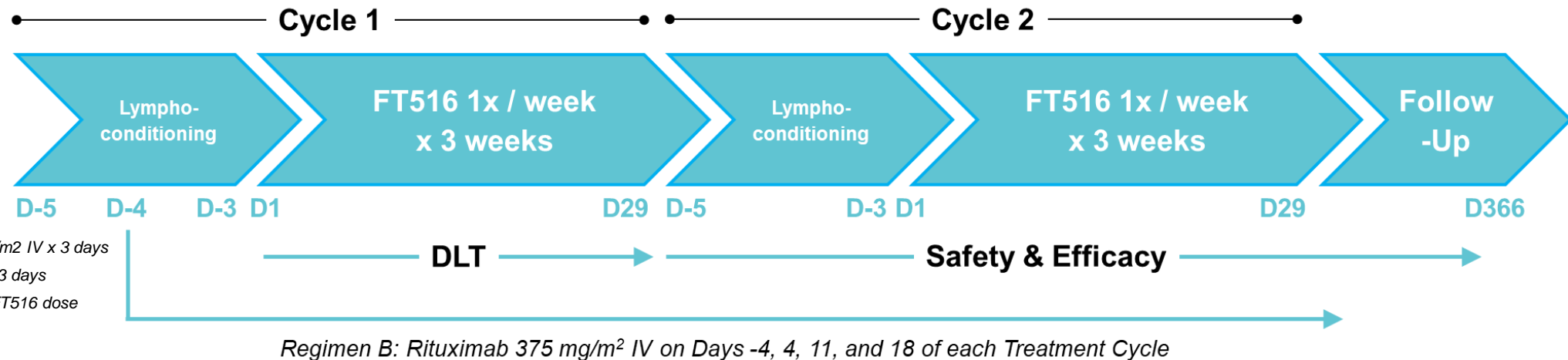
Median survival time for FT516 + anti-CD20
was not reached at Day 100

FT516 Universal, Off-the-Shelf hnCD16 NK Cell Product Candidate

Phase 1 Study Design: Multiple Doses over Multiple Cycles for AML & Lymphoma



First-ever Clinical Trial in World of Engineered iPSC-derived Cell Therapy



Regimen A – Monotherapy

- Relapsed / refractory AML
- Dose Escalation: 90M, 300M, 900M cells per dose
- Dose Expansion: up to 15 subjects

Regimen B – Rituximab Combination



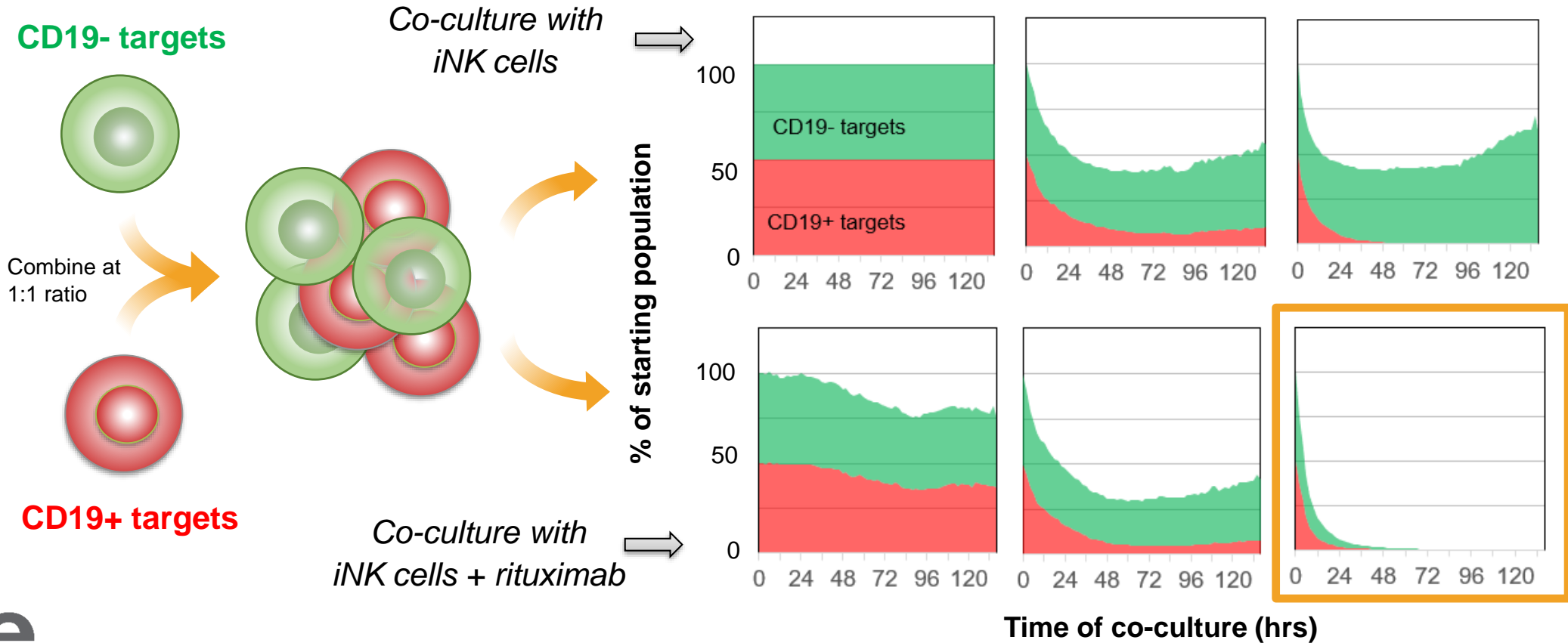
- Relapsed / refractory B-cell lymphoma
- Dose Escalation: 30M, 90M, 300M, 900M cells per dose + mAb
- Dose Expansion: up to 15 subjects

Targeting Multiple Tumor-associated Antigens

Leveraging *hnCD16* + CAR to Address Tumor Heterogeneity and Antigen Escape



Proprietary approach to drive deeper, more durable responses



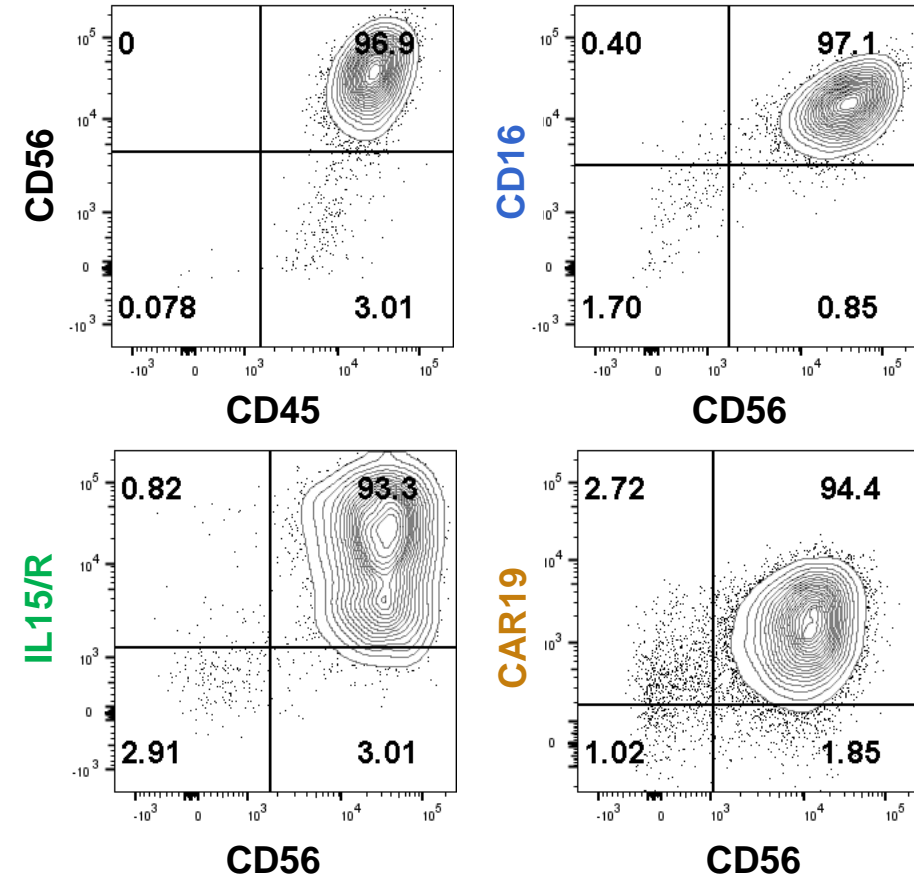
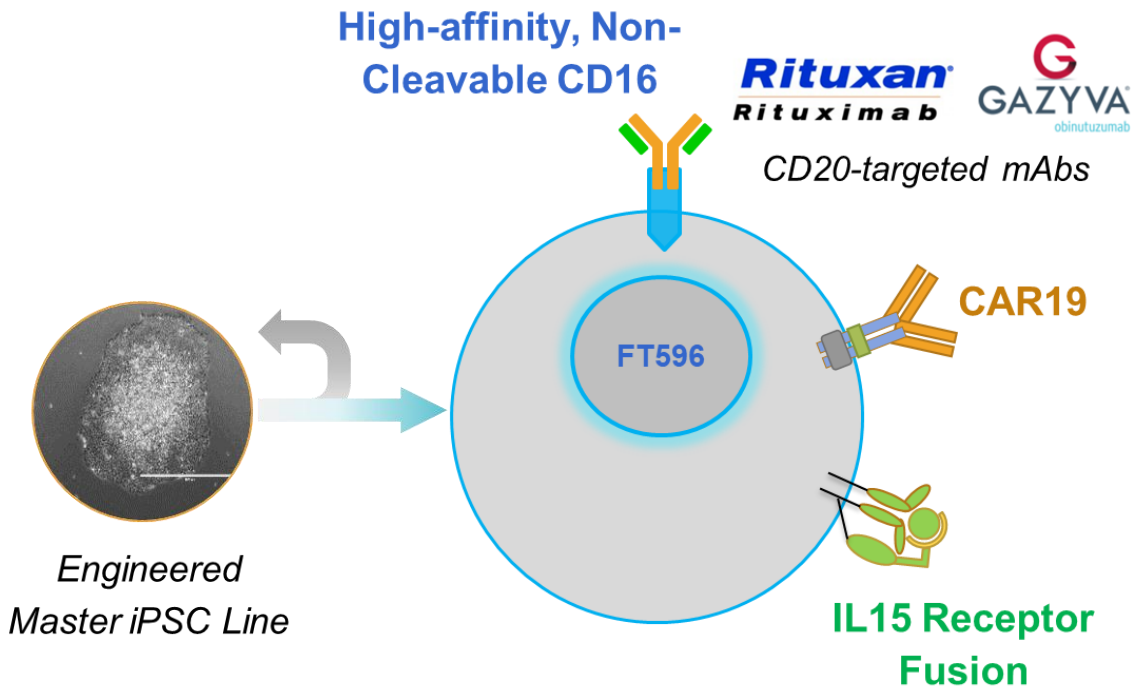
FT596 Universal, Off-the-Shelf Multi-Targeted CAR19 NK Cell Product

Potential Best-in-Class Product for B-cell Malignancies



Three Synthetic Elements: hnCD16 + CAR19 + IL15RF

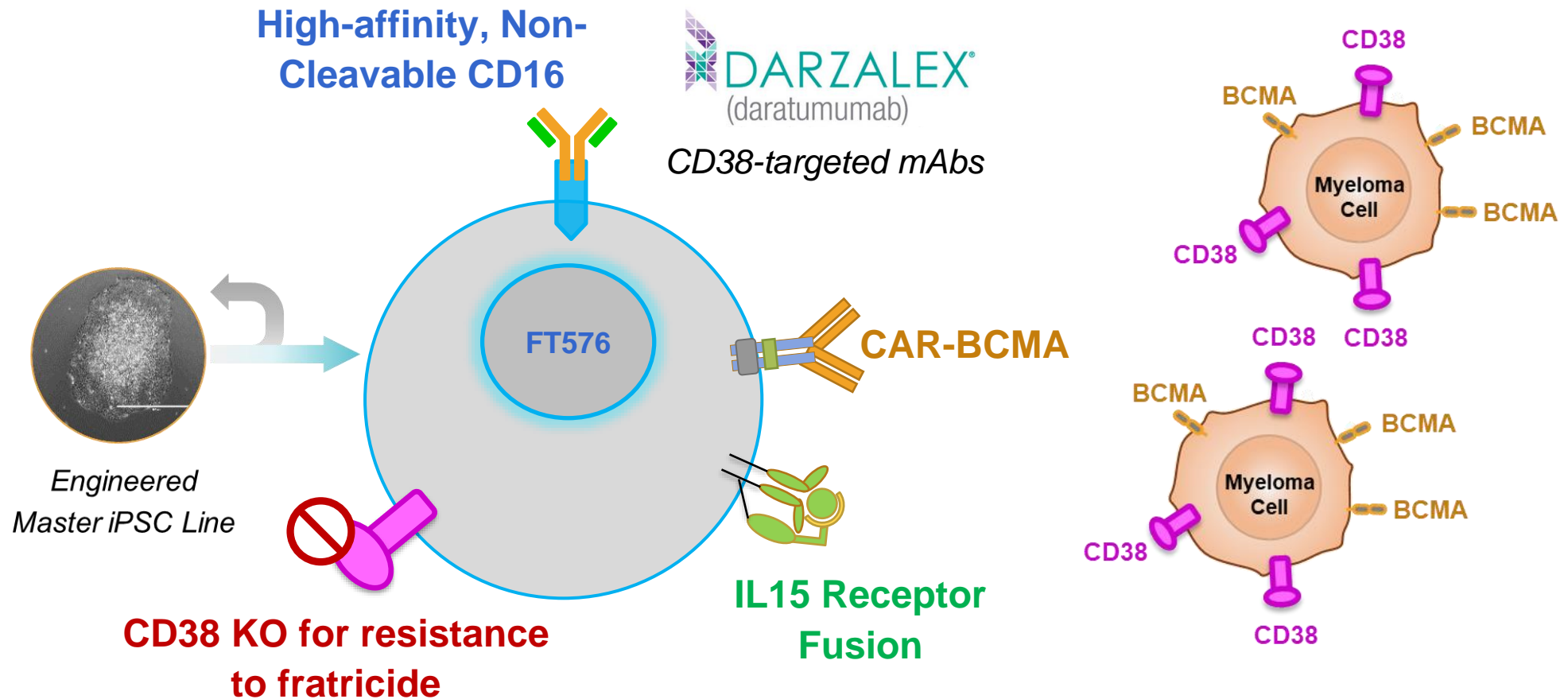
Uniformly Engineered Product Profile



FT576 Universal, Off-the-Shelf Multi-Targeted CAR-BCMA NK Cell Product

Potential Best-in-Class Product for Multiple Myeloma

Four Synthetic Elements: hnCD16 + CAR-BCMA + IL15RF + CD38KO



Universal, Off-the-Shelf CAR T-Cell Product Candidates

Memorial Sloan Kettering Collaboration



Dr. Michel Sadelain, MD, PhD
Director, Center for Cell Engineering
Memorial Sloan Kettering Cancer Center

LETTERS

Generation of tumor-targeted human T lymphocytes from induced pluripotent stem cells for cancer therapy

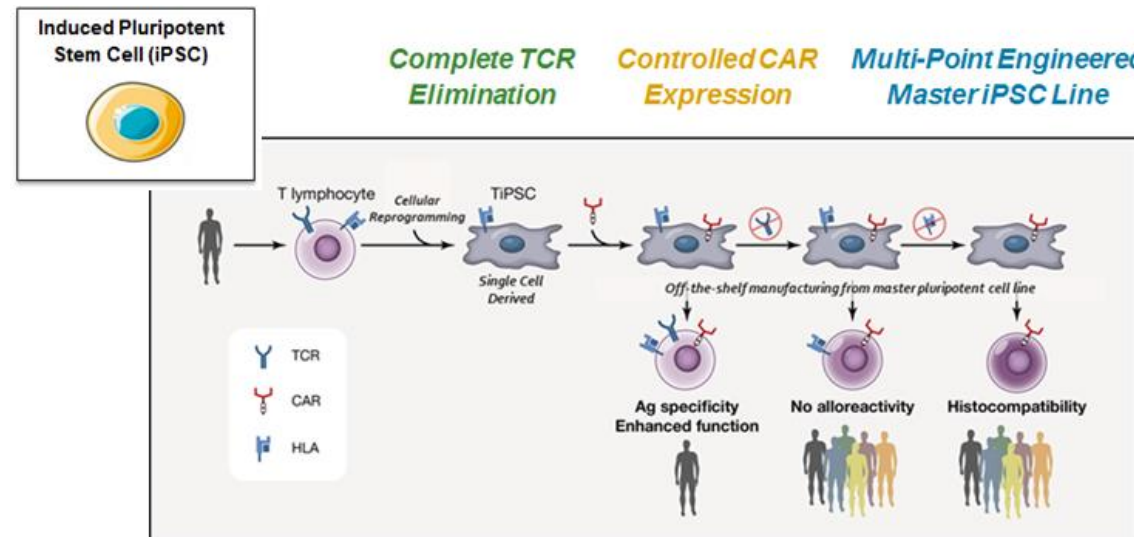
nature
biotechnology

Cell Stem Cell
Perspective



New Cell Sources for T Cell Engineering and Adoptive Immunotherapy

“Engineering therapeutic attributes into pluripotent cell lines is a breakthrough approach to renewably generate potent T-cell immunotherapies. This unique approach offers the prospect for off-the-shelf delivery of T-cell therapies with enhanced safety and therapeutic potential at the scale necessary to serve significant numbers of patients.”



Adapted from: Themeli, Riviere & Sadelain, Cell Stem Cells, 2015

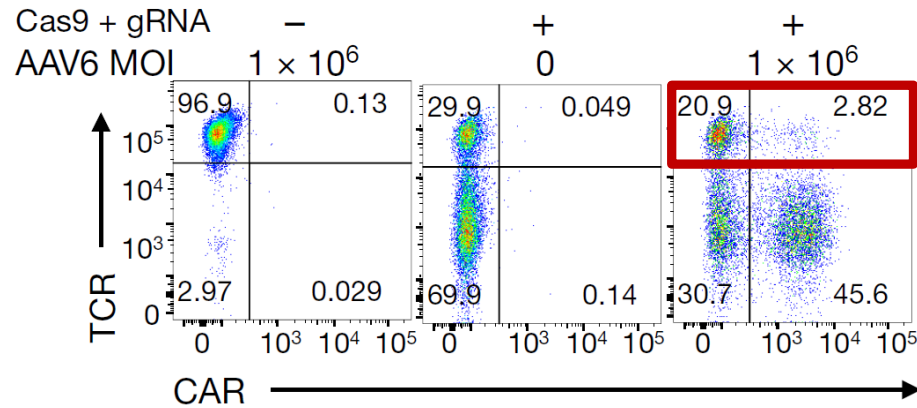
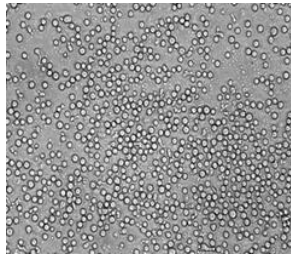
FT819 TRAC-encoded CAR 1XX Expression

Engineering Primary T Cells vs. Single iPSC Clone for TCR Elimination



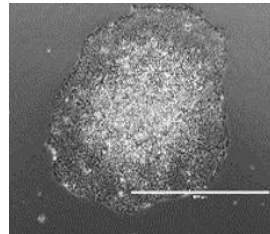
CRISPR Engineering: TCR Disruption + TRAC-encoded CAR Expression

Primary T Cell Batch

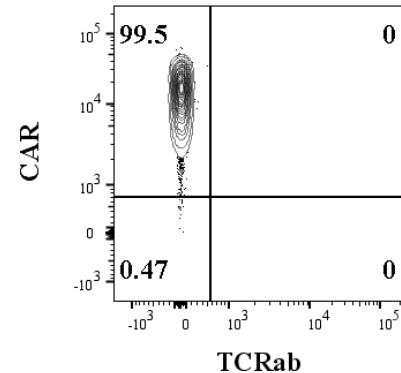


- ✓ 20% of T cells express allo-reactive TCR
- ✓ Only 45% of T cells have TCR KO + CAR expression

Single iPSC Clone



CAR-iT cell Profile

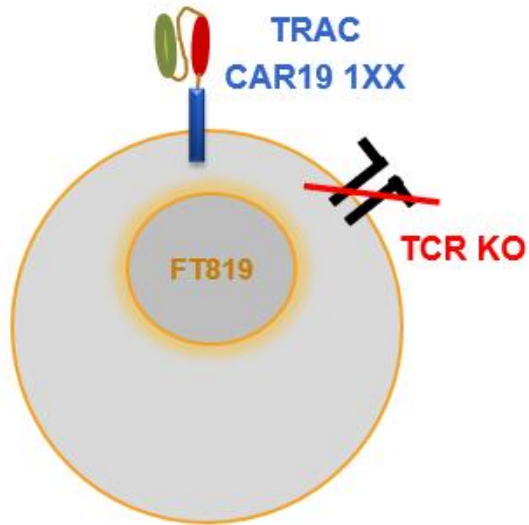


- ✓ Complete elimination of TCR expression
- ✓ Uniform and controlled CAR expression through TRAC

FT819 Universal, Off-the-Shelf CAR19 T-Cell Product

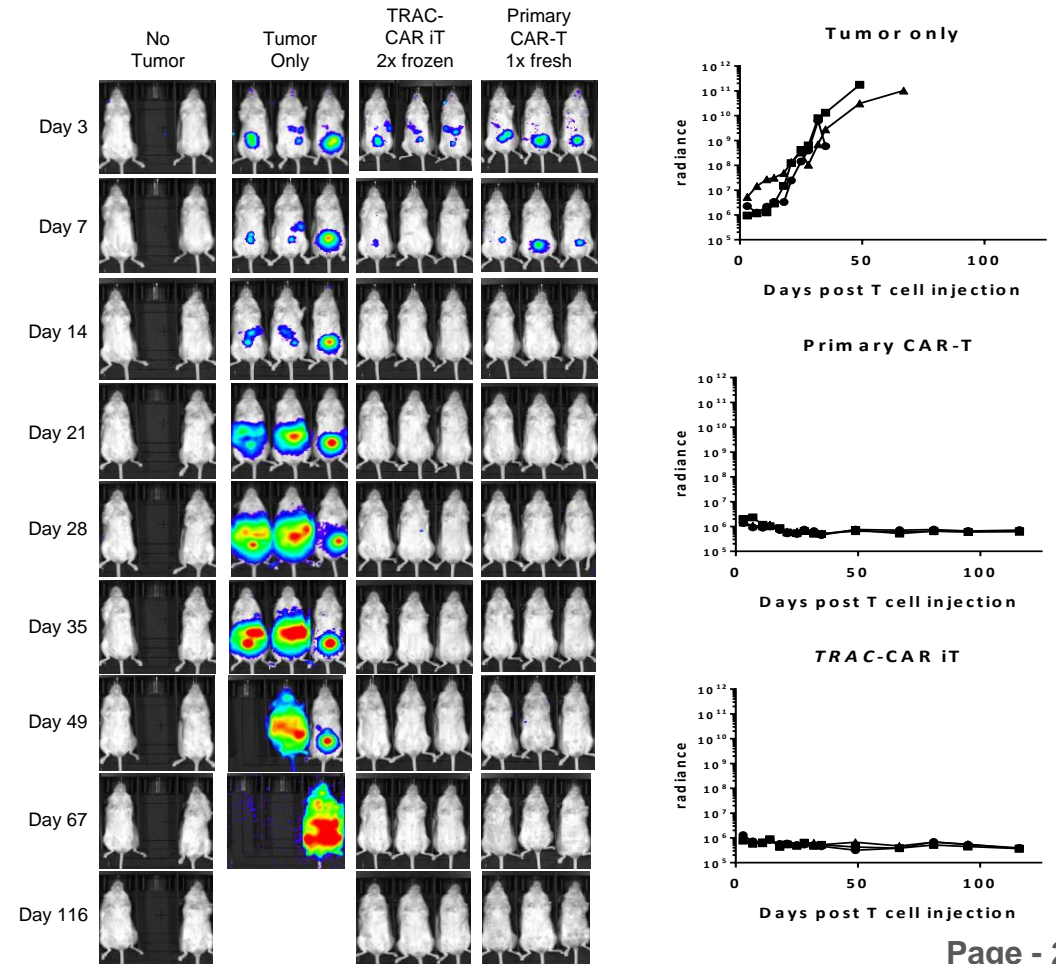
Novel CAR19 Targeted to the TRAC Locus for Improved Safety and Efficacy

Engineered CAR19 (1XX MSKCC) + TCR KO



- ✓ Novel CAR (MSKCC, 1XX) targeted to the TRAC locus for optimal activity
- ✓ Single cell derived, bi-allelic KO, iPSC clone for complete elimination of TCR mediated GvHD

Directly-infused *In Vivo* Anti-Tumor Activity





ONO Pharmaceutical Collaboration

Off-the-Shelf iPSC-derived CAR T-Cell Product Candidates



	Product 1 CAR T-cell targeting Antigen “ND”	Product 2 CAR T-cell targeting Antigen “ND”
Tumor Type	Lymphoblastic leukemia	Solid tumor
Binding Domain	FATE to contribute	ONO to contribute
Preclinical Funding	Up to \$70M, including \$10M upfront plus \$20M in committed research funding and up to an additional \$40M in contingent fees	
ONO Rights (subject to Preclinical Option Exercise)	Asia only	WW with FATE having opt-in right to develop and commercialize in the U.S. and Europe under a 50-50 profit-sharing arrangement
Post-Option Economics	Up to \$285M in clinical development, regulatory and sales milestones plus royalties	Up to \$895M in clinical development, regulatory and sales milestones plus royalties

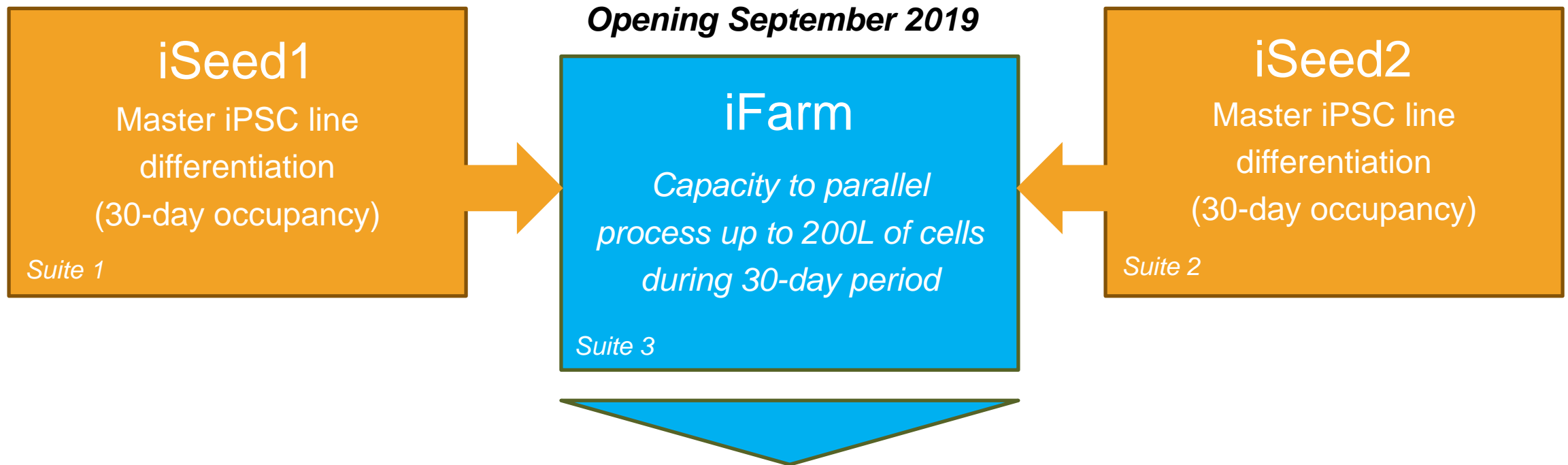
ND = Not publicly disclosed

Mass Production of iPSC-derived Cellular Immunotherapies

Design of In-house Manufacturing Facility



A simple, scalable and modular GMP facility to support cost-effective production of multiple product candidates in parallel



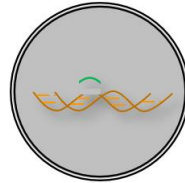
~600 doses, across 1-2 product candidates, per month

iPSC Product Platform

Clonal Master iPSC Lines for Off-the-Shelf Cell Products



Single
iPSC Clone



(Engineered) Single Pluripotent Stem Cell

- Renewable
- Potential to differentiate into 200+ cell types



Unlimited Supply of
Clonal Master iPSC
Lines

Master Cell
Bank



Working Cell Banks
Working Cell Banks
Working Cell Banks



Thousands of
Clonally-derived Doses
of Cell Products



**Off-the-Shelf
Homogeneous | Multi-Dosing
(Engineered) Cell Products**



“to reach more patients in need”

Next-Generation Cell-based Cancer Immunotherapy

Therapeutic Vision for Long-Term Durable Responses



Intervention Strategy

Profile of Next-Generation Cell Products

Early

- Differentiated safety profile
- Well-tolerated regimens

Often

- Multi-dose, multi-cycle treatments
- Cost-effective manufacture

Combinations

- Augment established agents' MOA
- Incorporate and deliver multiple MOAs

Financial Summary

As of March 31, 2019



Three Months Ended March 31, 2019	
Revenue	\$2.6M
Operating Expense, Adjusted ¹	\$19.2M
Cash & Cash Equivalents	\$183.5M
Employees	125
Total Shares Outstanding ²	79.3M

[1] Excludes non-cash stock-based compensation expense of approximately \$3.9M.

[2] Includes 14.1M shares of common stock from conversion of non-voting preferred stock.

