AACR American Association for Cancer Research®

FINDING CURES TOGETHER®

GENERATION OF OFF-THE-SHELF TCR-LESS CAR T CELLS FROM RENEWABLE PLURIPOTENT CELLS

Bob Valamehr, PhD

Vice President, Fate Therapeutics

AACR Annual Meeting 2018 Press Program
McCormick Place North/South
Chicago, IL
April 14-18, 2018

FINANCIAL RELATIONSHIPS AND CONFLICTS OF INTEREST

Bob Valamehr is an employee of Fate Therapeutics

THE RISE AND APPROVAL OF CAR T-CELL THERAPY

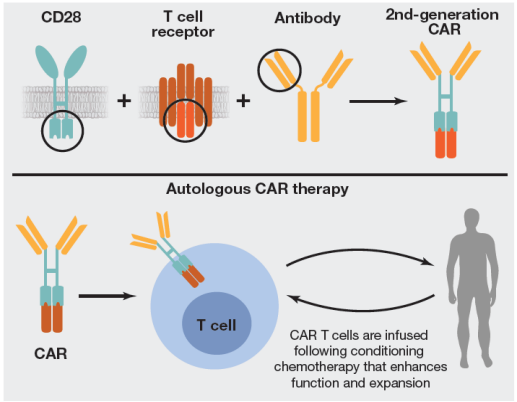
Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRζ /CD28 receptor

John Maher, Renier J. Brentjens, Gertrude Gunset, Isabelle Rivière, and Michel Sadelain*

Leading Edge
Bench to Bedside
Cell

CD19 CAR T Cells

Michel Sadelain
Center for Cell Engineering, Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY 10065, USA
Correspondence: m-sadelain@ski.mskcc.org
http://dx.doi.org/10.1016/j.cell.2017.12.002



HEALTH & HUMAN SERVICES • USA
FDA

FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute

FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma

Yescarta is the second gene therapy product approved in the U.S.

KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion

YESCARTA™ (axicabtagene ciloleucel) Suspension for IV infusion

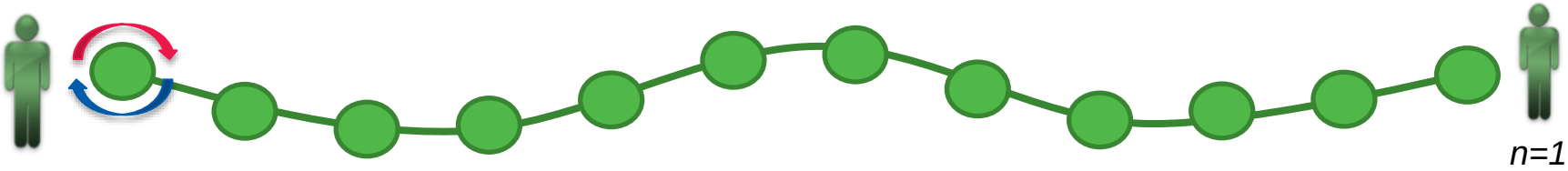
CAR T-CELL THERAPY – GENERATION 1.0

American Association for Cancer Research®
FINDING CURES TOGETHER®

Autologous CAR T-Cell Therapy

NOVARTIS Kite JUNO THERAPEUTICS

Different Starting Material Every Time



n=1

Patient Identification

Apheresis Collection

Collection Bar Coding

Shipment to Process Center

Confirmation of Specification

T Cell Selection and Activation

Pool Expansion

Pool Genetic Editing

Desired T Cell Enrichment

Completion of Manufacturing

Banking of Single Dose and Release

Shipment to Infusion Center and Infusion

Impaired Starting Material | Random & Variable T-Cell Engineering | Complex Logistics

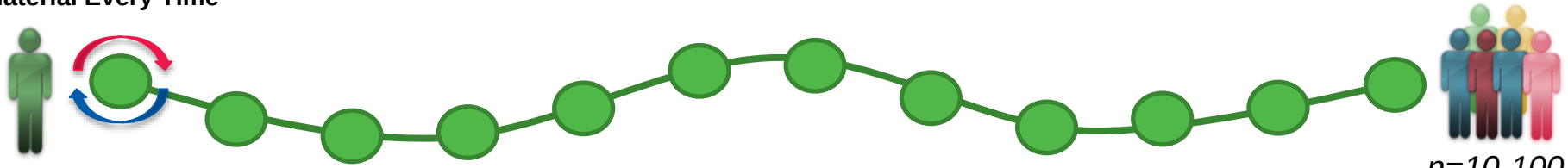
Single Dose Paradigm | Heterogeneous Drug Product | Expensive

CAR T-CELL THERAPY – GENERATION 1.1

American Association for Cancer Research®
FINDING CURES TOGETHER®

Allogeneic CAR T-Cell Therapy

Different Starting Material Every Time



Donor Identification

Apheresis Collection

Collection Bar Coding

Shipment to Process Center

Confirmation of Specification

T Cell Selection and Activation

Pool Expansion

Pool Genetic Editing

Desired T Cell Enrichment

Completion of Manufacturing

Banking of Multiple Doses and Release

Shipment to Infusion Center and Infusion

n=10-100

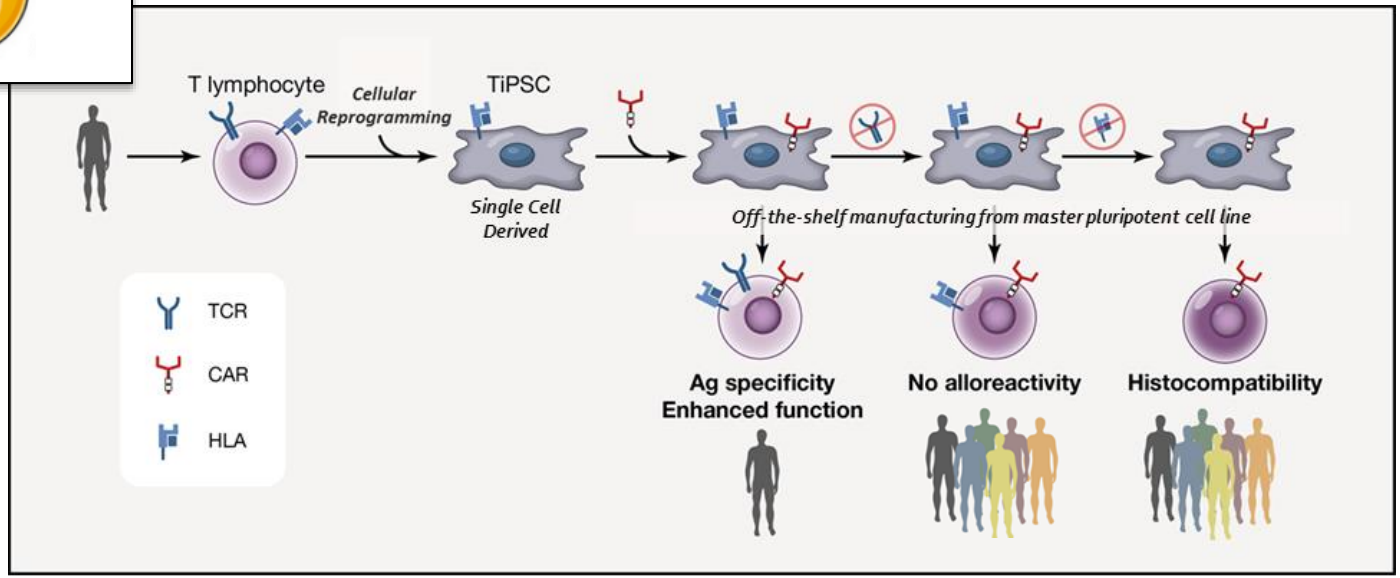
Healthy Starting Material | Random & Variable T-Cell Engineering | Complex Logistics

Multiple Dose Paradigm | Heterogeneous Drug Product | Expensive

CAR T-CELL THERAPY –
THE OFF-THE-SHELF VISION

Induced Pluripotent Stem Cell (iPSC)

Complete TCR Elimination ***Controlled CAR Expression*** ***Multi-Point Engineered Master iPSC Line***



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

CAR T-CELL THERAPY – GENERATION 2.0

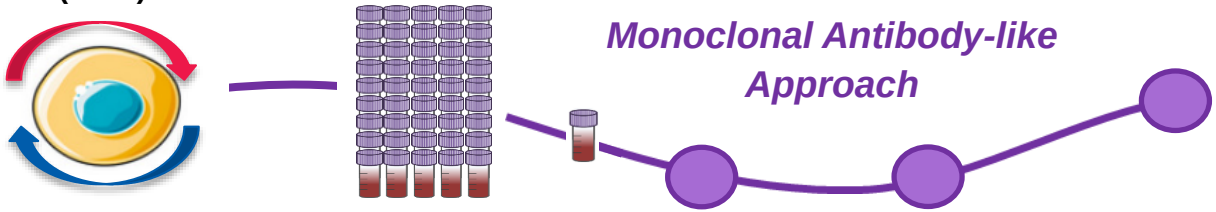
American Association for Cancer Research
FINDING CURES TOGETHER

Off-the-Shelf CAR T-Cell Therapy

Fate THERAPEUTICS

Memorial Sloan Kettering Cancer Center

Single Induced Pluripotent Stem Cell (iPSC)



Monoclonal Antibody-like Approach

n = 100s-1000s

Engineering and Selection of iPSC Clone | **Master iPSC Lines & Cell Bank** | **iPSC-to-T Cell Manufacture** | **Banking of Multiple Doses and Release** | **Shipment and Infusion**

Healthy Banked Starting Material | One-time Uniform iPSC Engineering | Scalable Logistics

Multiple Dose Paradigm | Homogeneous Drug Product | Cost-Effective

MASTER IPSC LINE

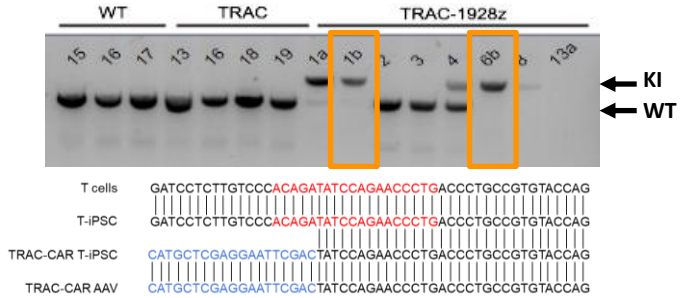
ELIMINATION OF TCR | CONTROLLED CAR EXPRESSION

American Association for Cancer Research®
FINDING CURES TOGETHER®

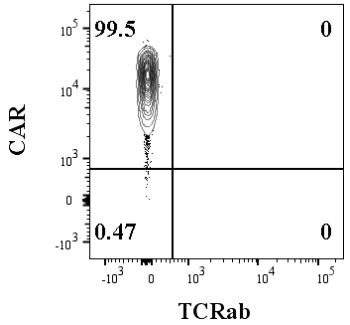
One-time Editing Event

Single iPSC

Genomic Assessment



Phenotypic Assessment

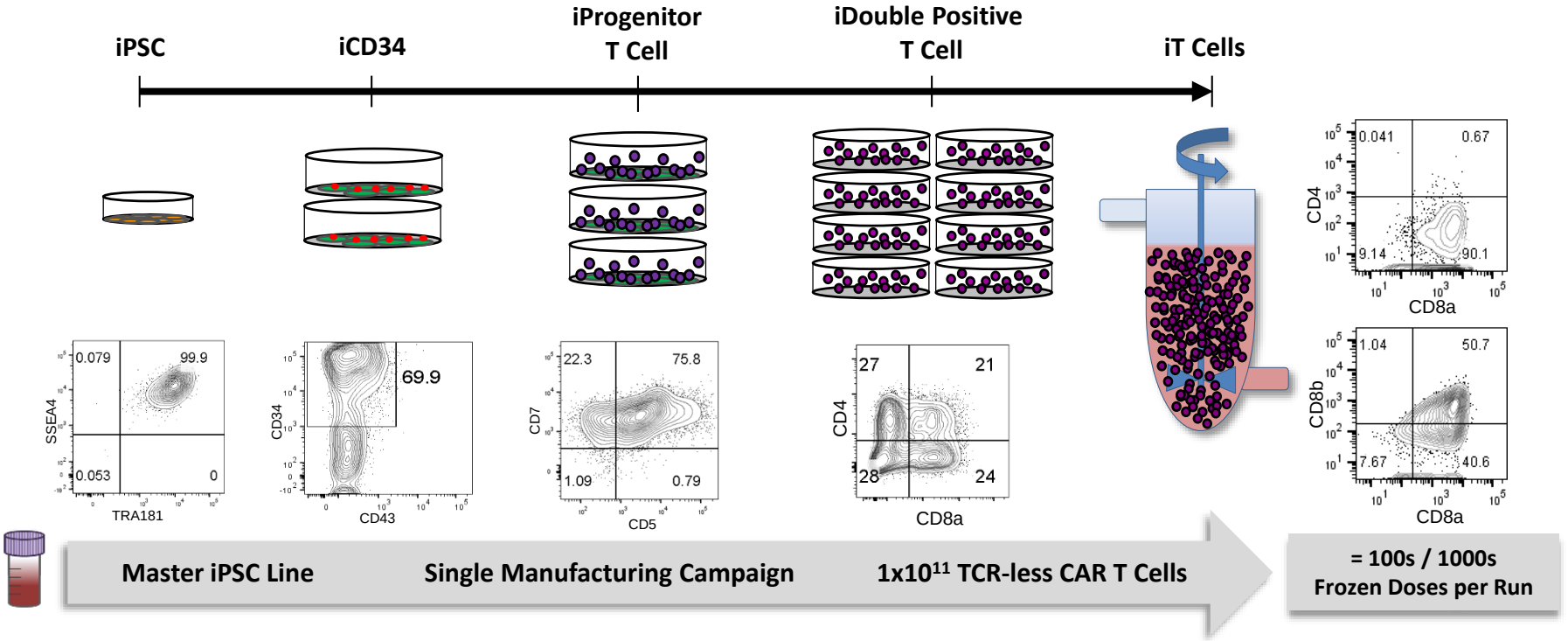


Complete Elimination of TCR Expression

PRODUCTION OF TCR-LESS CAR T CELLS

MASTER IPSC LINE FOR T-CELL PRODUCTION

American Association for Cancer Research®
FINDING CURES TOGETHER®



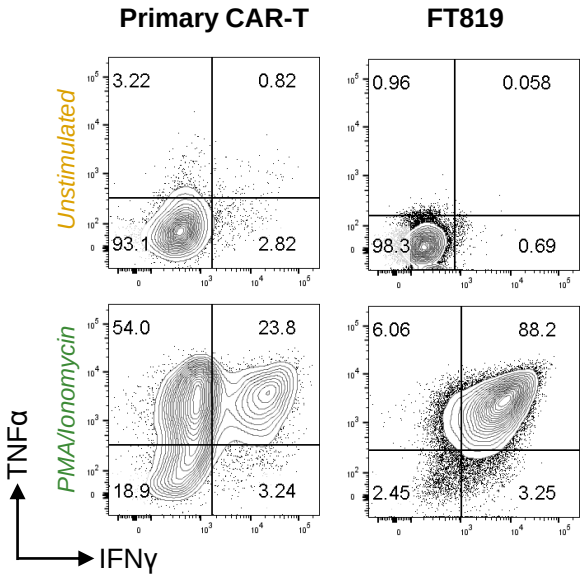
FT819 – CAR19 ACTIVITY

RESPONSIVE | CYTOTOXIC | SPECIFIC

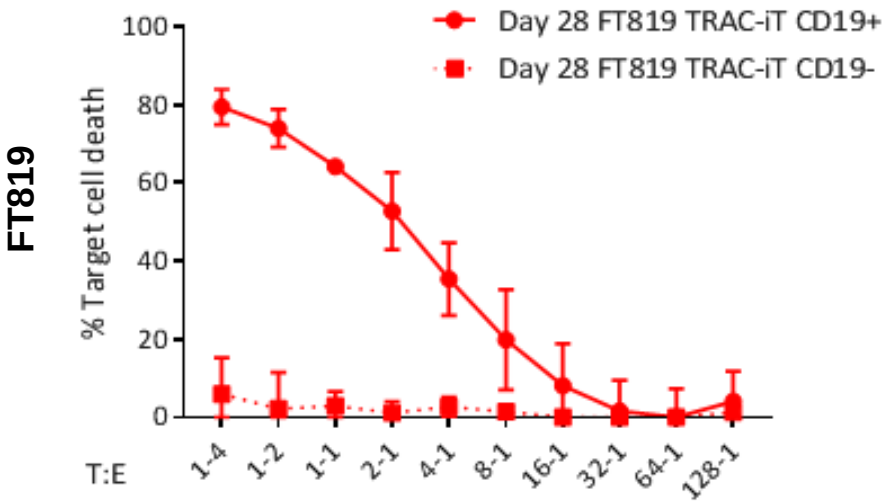
American Association for Cancer Research®

FINDING CURES TOGETHER®

Cytokine Production

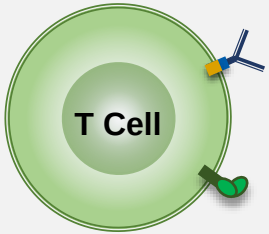


Antigen-specific Cytotoxicity



FT819 – CD16 FC RECEPTOR ACTIVITY

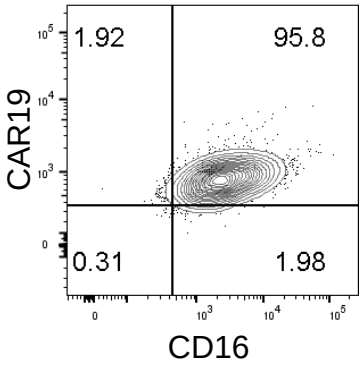
MITIGATING ANTIGEN ESCAPE THROUGH ADCC



CAR19 – CD19 antigen targeting

CD16 – universal engager for antibody-dependent cellular cytotoxicity (ADCC)

FT819

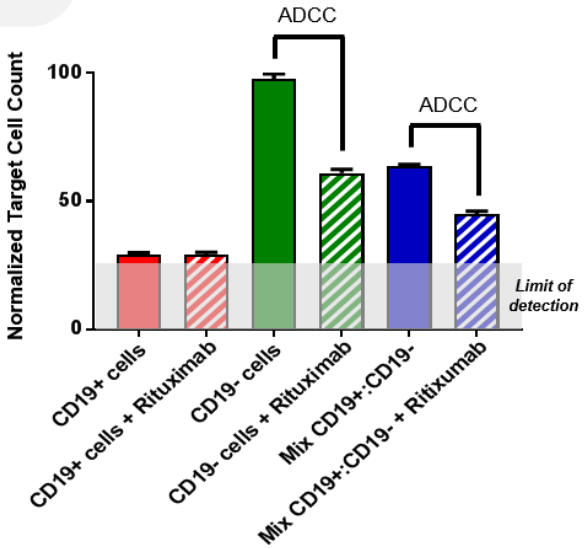


100% CD19+ cells

100% CD19- cells

50:50 CD19+:CD19- mixture

FT819 + / - Rituximab

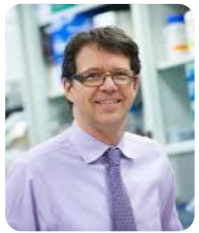


CONCLUSION / ACKNOWLEDGEMENT

- CAR T cells can be robustly manufactured from a multi-point engineered master iPSC line
- The master iPSC line is self-renewing and can be used repeatedly without sourcing new donor material or re-engineering cells
- A single manufacturing campaign yields large quantities of CAR T cells
- We are developing FT819, an off-the-shelf T cell therapy which completely lacks TCR expression, has controlled CAR19 expression through TRAC insertion and has CD16 expression for ADCC
- **FT819 is an off-the-shelf CAR T cell therapy with the potential to improve safety and efficacy, address antigen escape, broaden patient accessibility and reduce cost of manufacture and delivery**

Fate THERAPEUTICS

Memorial Sloan Kettering Cancer Center™



Michel Sadelain, MD, PhD

Isabelle Rivière, PhD