

Off-the-Shelf Dual-CAR T-Cell Therapy: Targeting B and T Cells in Autoimmune Disease Without Preconditioning

Natalie J. Shiff,¹ Mark Jelcic,¹ Shilpi Chandra,¹ Soheila Shirinbak,¹ Brian Groff,¹ Alma Gutierrez,¹ Miguel Meza,¹ Bjoern Gaertner,¹ Karina Palomares,¹ Loraine Campanati,¹ Carissa Dege,¹ Pei Fang Tsai,¹ Tom Lee,¹ Raedun Clarke,¹ Andrew BitMansour,¹ Karl-Johan Malmberg,^{2,3} Maksim Mamonkin,⁴ Bahram Valamehr,¹ Vaneet K. Sandhu,¹ Alex Garcia,¹ Martin Hosking¹

¹Fate Therapeutics, Inc., San Diego, CA; ²Karolinska Institute, Stockholm, Sweden; ³Oslo University Hospital, Oslo, Norway; ⁴Columbia University, New York, NY USA

Background

iPSC-derived T cells overcome the challenges associated with autologous CAR T-cell therapies and allow for broad patient access

Autologous CAR T-cell therapies involve prolonged pre- and post-apheresis timelines, with limited access to treatment centers, drug product inconsistency, high cost, and limited production capacity.

A scalable iPSC platform addresses these key limitations:

Platform Advantages

- **Defined Clonal Master Cell Bank (MCB):** Single-cell derived, genetically uniform, selected for potency and genomic integrity
- **Engineered MCB Starting Material:** Highly scalable, donor-independent, and consistent high-quality product
- **Modular Innovation:** Accelerates development through multiplexed precision engineering

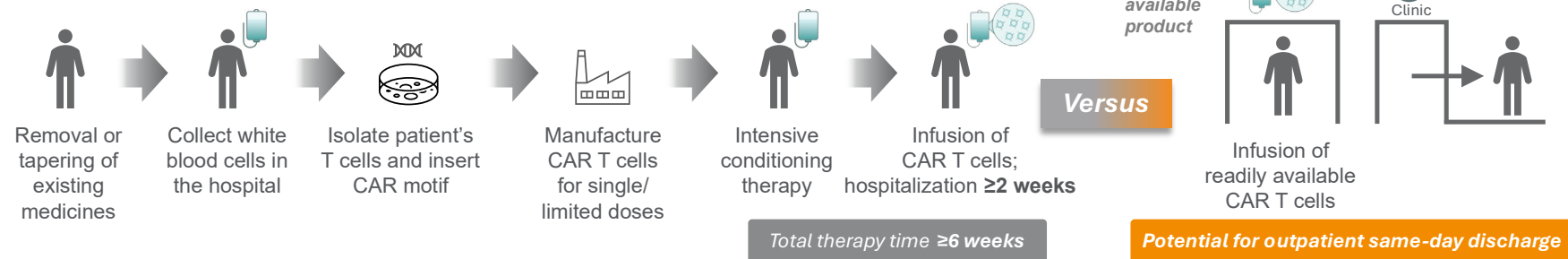
iPSC-Derived Cell Therapy Products

- **Reliable, Scalable Drug Product:** Consistent, well-characterized, >5-year shelf stability
- **Cost-Effective & Consistent:** Low cost of goods, inventory-based economics, and no donor variability
- **Patient-Centered Therapy:** Off-the-shelf with potential for outpatient administration

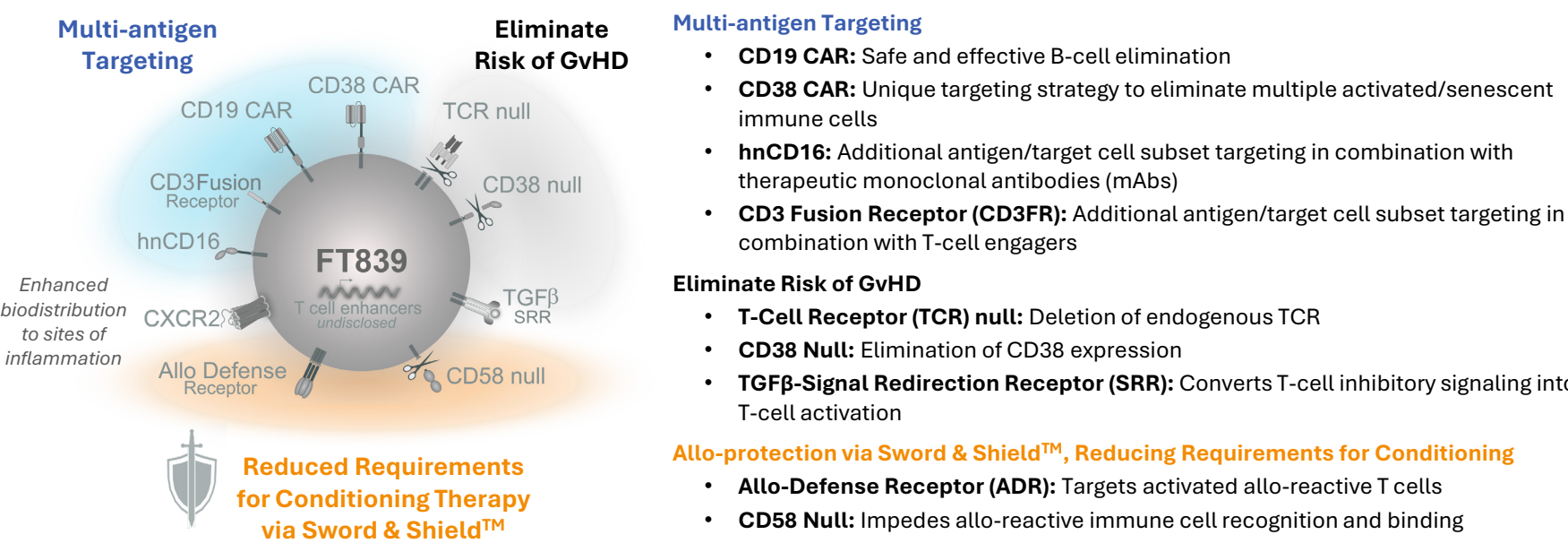
Delivery of Conventional Versus Off-the-Shelf, iPSC-derived CAR T-Cell Therapy

Conventional Autologous CAR T-Cell Therapy

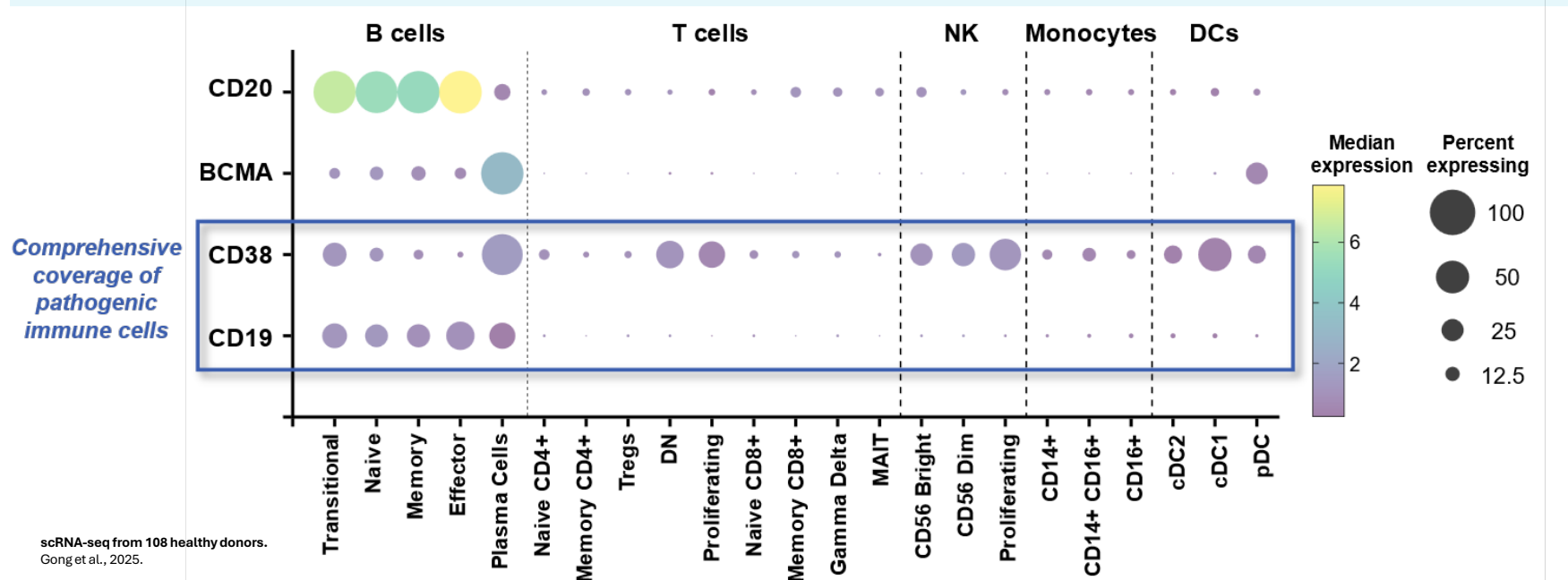
Not available on-demand



FT839 is a dual CD19 and CD38 CAR T cell targeting multiple immune cell types with the potential to reduce the need for conditioning therapy



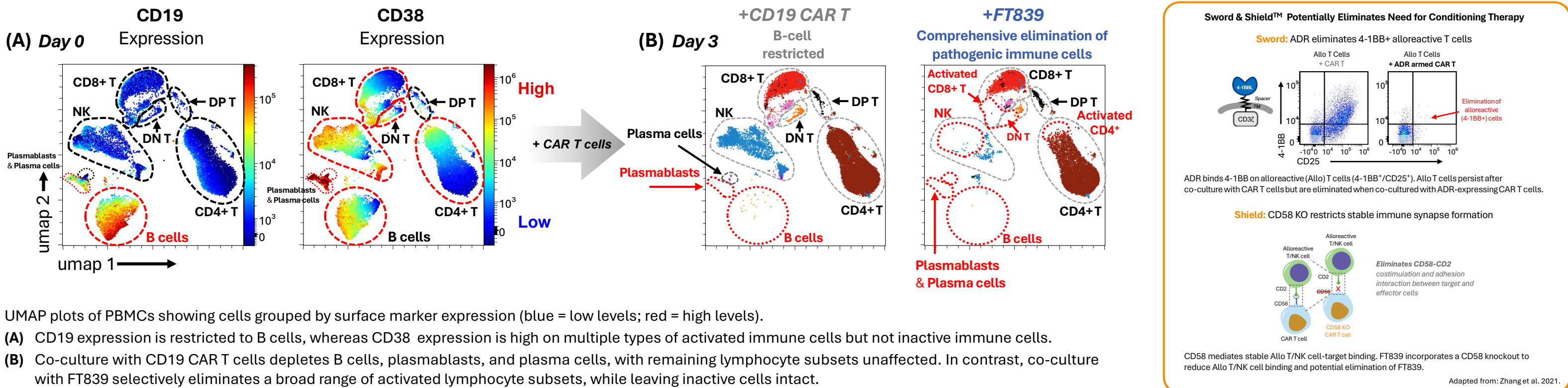
Targeting B-cell lineage (CD19) and activated immune cells (CD38) for a comprehensive approach to treat autoimmune diseases



- **Current CAR-T approaches:** Primarily B-cell targeting via CD19 and/or B-cell maturation antigen (BCMA)
- **Complex autoimmune disease:** Multiple activated immune cells beyond B cells, including activated T and NK cells
- **CD38:** Selectively expressed on activated immune cells, including proliferating and double-negative T cells implicated in disease; absent on inactive cells
- **CD19 and CD38 targeting:** Potential elimination of pathogenic immune cells, including B cells and activated T cells
- **Potential advantage:** Preservation of the inactive immune cell repertoire

Results

FT839 eliminates B cells and selectively eliminates activated immune cells while potentially reducing the need for conditioning therapy in PBMC co-cultures

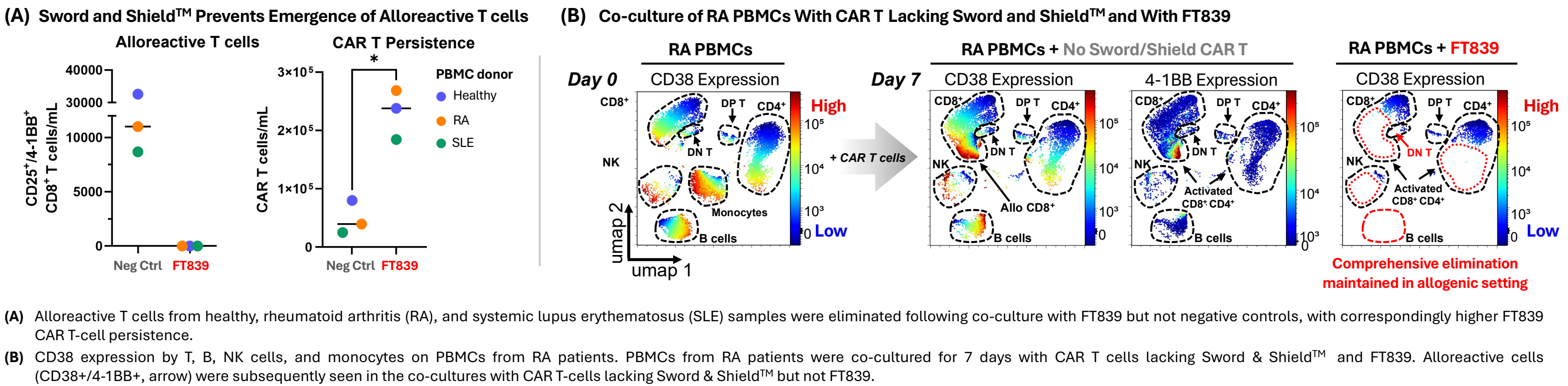


UMAP plots of PBMCs showing cells grouped by surface marker expression (blue = low levels; red = high levels).

(A) CD19 expression is restricted to B cells, whereas CD38 expression is high on multiple types of activated immune cells but not inactive immune cells.

(B) Co-culture with CD19 CAR T cells depletes B cells, plasmablasts, and plasma cells, with remaining lymphocyte subsets unaffected. In contrast, co-culture with FT839 selectively eliminates a broad range of activated lymphocyte subsets, while leaving inactive cells intact.

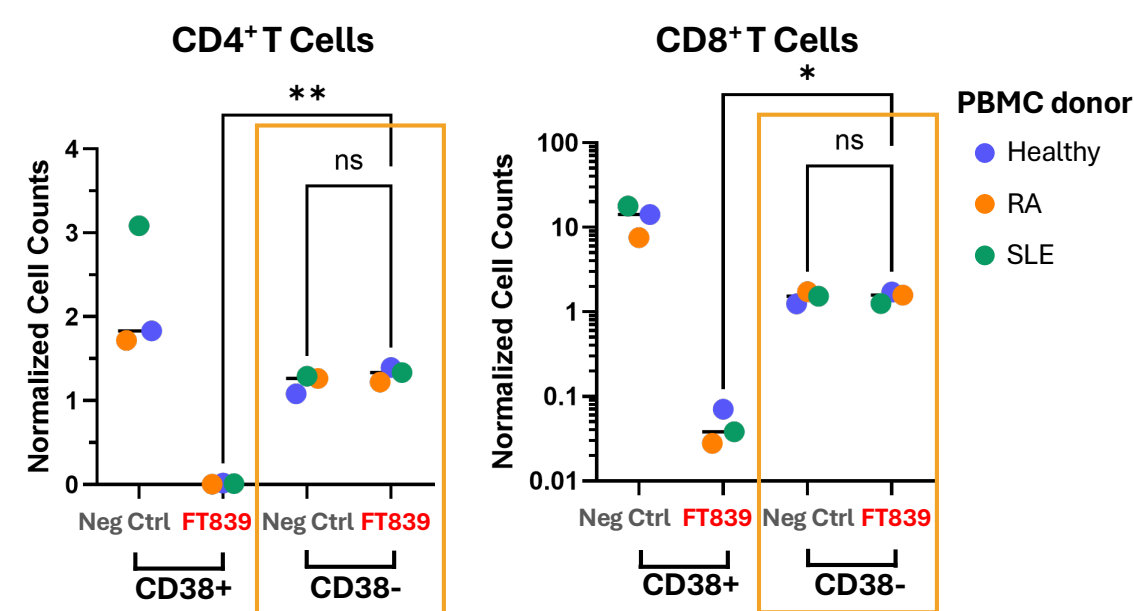
FT839 increases CAR T-cell persistence and selectively eliminates activated immune cells in RA patient samples in an allogeneic setting



(A) Alloreactive T cells from healthy, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) samples were eliminated following co-culture with FT839 but not negative controls, with correspondingly higher FT839 CAR T-cell persistence.

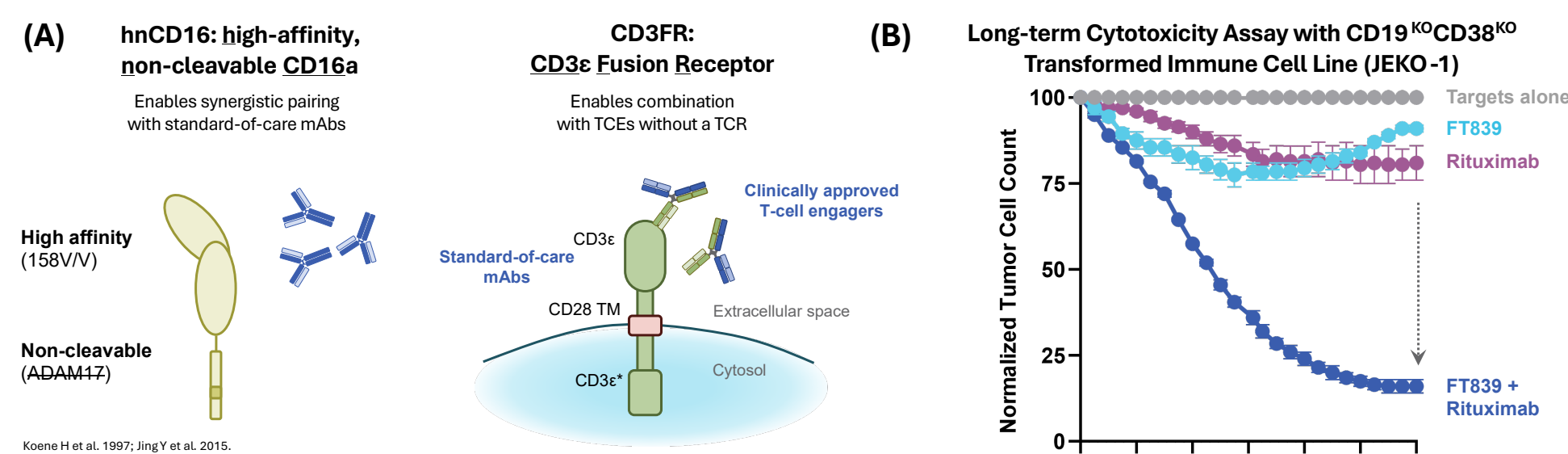
(B) CD38 expression by T, B, NK cells, and monocytes on PBMCs from RA patients. PBMCs from RA patients were co-cultured for 7 days with CAR T cells lacking Sword & Shield™ and FT839. Alloreactive cells (CD38+/4-1BB+, arrow) were subsequently seen in the co-cultures with CAR T-cells lacking Sword & Shield™ but not FT839.

FT839 selectively eliminates activated T cells



- Activated (CD38+) T-cell subsets (CD4+ and CD8+) were selectively eliminated by FT839+.
- Inactive (CD38-) T cells were observed at levels similar to those in the negative controls.

Pairing with clinically approved biologics extends disease cell targeting capabilities



Multi-antigen Targeting in Combination With T-Cell Engagers and mAbs

- (A) hnCD16 enables FT839 binding of the Fc region of mAbs, leading to FT839 activity independent of CD19/CD38 expression.
- (B) As a CD19 and CD38 null transformed immune cell line, JEKO-1 cells do not express the primary targets of FT839. Through hnCD16, FT839 is uniquely capable of targeting this CD19^{KO}/CD38^{KO} cell line in the presence of the mAb rituximab, with synergistic effect. Similar results are seen in the presence of a TCE via interaction with the CD3FR on the FT839 cell surface (data not shown).

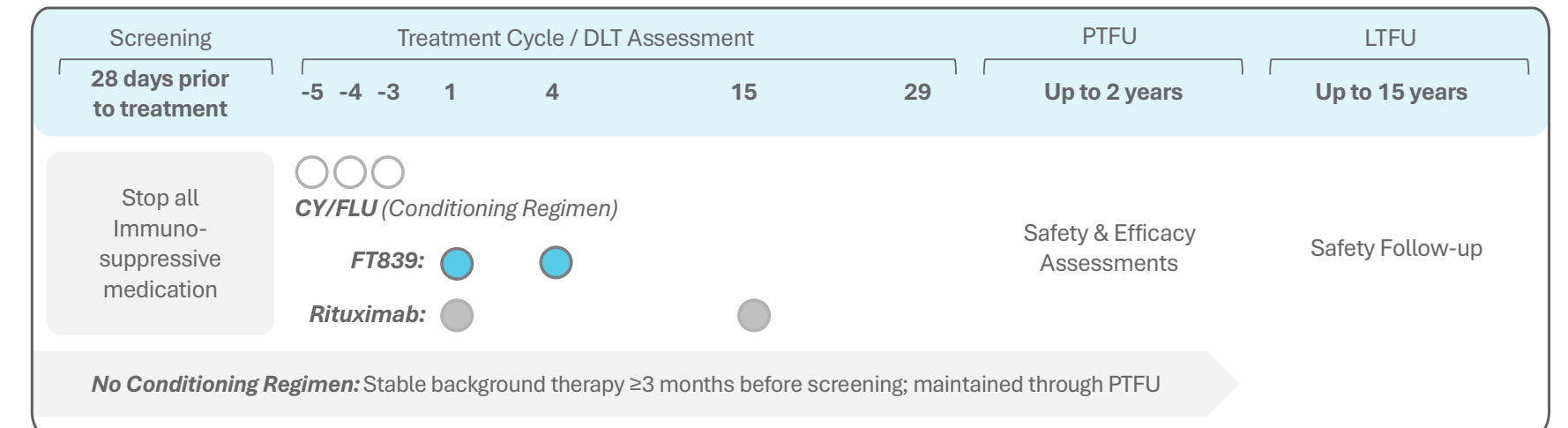
Phase 1/2 Basket Trial of FT839 in Autoimmune Disease

COMPLETE Trial: Designed to enable accelerated development across multiple indications, including RA, from dose escalation and expansion to Phase 2 cohorts

This Phase 1/2 dose-escalation and dose-expansion basket trial is evaluating the safety, PK, anti-B-cell activity, and clinical activity of FT839 in participants with moderate-to-severe autoimmune diseases, including RA (NCT07800871).

Treatment approaches being evaluated include:

- **No Conditioning Regimen:** FT839 (Days 1 & 4) + rituximab (Days 1 & 15) + stable background therapy
- **Conditioning Regimen:** CY/FLU conditioning for 3 days prior to FT839, followed by FT839 (Days 1 & 4) + rituximab (Days 1 & 15); conditioning with bendamustine permitted with medical monitor approval



CY/FLU = cyclophosphamide/fludarabine. Post-treatment follow-up (PTFU) is up to 2 years from Day 1, followed by long-term follow-up (LTFU) for up to 15 years from Day 1.

Key Inclusion Criteria:

- Age 18–70 years
- Confirmed active autoimmune disease
- Moderate-to-severe disease with intolerance/inadequate response to ≥2 prior therapies
- Adequate organ function
- Ability to provide informed consent and comply with study procedures

Key Exclusion Criteria:

- >1 disease under study/overlap syndrome
- Pregnancy or lactation
- Significant cardiac, pulmonary, hepatic, or renal impairment
- Active/chronic infection or recent malignancy
- Prior CAR T-cell therapy, organ transplantation, or recent anti-CD19/CD20 therapy (<6 months)
- Allergy to study treatments
- Body weight <45 kg
- Active/recent CNS manifestations (<12 months)

Conclusion

FT839: Anti-CD19/CD38 Dual CAR T-Cell Product Candidate

Multi-Antigen Targeting

- CD19 CAR, CD38 CAR, hnCD16, CD3FR with potential for:
 - Use in complex autoimmune diseases involving multiple cell types
 - Deeper B-cell depletion
 - Ability to synergize with monoclonal antibodies (such as rituximab) or T-cell engagers

Stealth Technology

- Sword & Shield™ for resistance to alloreactive T cells and reduced requirement for conditioning therapy

Platform Advantage

- iPSC allows for uniform quality, mass production, and off-the-shelf availability, increasing accessibility with potential for future outpatient administration

Phase 1/2 Trial

- A first-in-human Phase 1/2 basket trial targeting autoimmune diseases with multiple immune cell disease drivers, including RA, is open for enrollment

References: Gong et al., *Nature*. 2025; 648:696–706; Jing et al., *PLoS One*. 2015; 10; Koene et al., *Blood*. 1997; 90:1109–14; Zhang et al., *Front Immunol*. 2021; 12:705260.
Abbreviations: ADR = Allo-defense receptor; BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; CNS = central nervous system; FR = fusion receptor; GvHD = graft-versus-host disease; hnCD16 = high-affinity, non-cleavable CD16; iPSC = induced pluripotent stem cell; mAb = monoclonal antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SRR = signal redirection receptor; TCR = T-cell receptor; UMAP = Uniform Manifold Approximation and Projection.

Presented at Congress of Clinical Rheumatology – West 2026. September 17–20, Huntington Beach, CA. **Sponsored by Fate Therapeutics, Inc.**

Disclosures: Presenting Author, Andrew BitMansour; Lead Investigator, Martin Hosking; employees and stockholders of Fate Therapeutics, Inc.