Targeting of Tumor Antigen CD38 and Stress Antigens MICA/B by CAR T cells Provides a Unique Approach for the Comprehensive Treatment of Multiple Myeloma

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Introduction

Recently approved autologous chimeric antigen receptor (CAR) T-cell therapies (Abecma® and Carvykti®) have demonstrated clear clinical benefit for patients with relapsed/refractory multiple myeloma (MM) with initial response rates ranging between 73-98%. Unfortunately, many of these patients ultimately relapse, often as the result of antigen shedding and tumor heterogeneity, tumor microenvironment suppression, and poor CAR T-cell functional persistence, highlighting the need for alternative therapies that can simultaneously mitigate and overcome these tumor-intrinsic and -extrinsic challenges. Furthermore, broad patient access of patient- and donor-derived CAR T cells are limited by manufacturing challenges and the use of conditioning chemotherapy.

FT836 is an iPSC-derived CAR T cell that uniquely targets the conserved α3 domain of the inducible stress ligands MICA/B, enabling broad recognition of both hematologic and solid tumors. The unique engineered elements of FT836 further enable (i) multi-antigen targeting by antibody-dependent cellular cytotoxicity (ADCC) in combination with the high-affinity non-cleavable CD16a Fc receptor (hnCD16) and therapeutic monoclonal antibodies (e.g. sarclisa and daratumumab), (ii) functional persistence in an allogeneic setting without the reliance on conditioning chemotherapy using dual Sword and Shield™ engineering, incorporating a synthetic alloimmune defense receptor (ADR) that selectively eliminates 4-1BB+ alloreactive immune cells and genetic deletion of CD58 to avoid recognition by host immune cells, and (iii) improved tumor homing and resistance to immunosuppression via expression of the chemokine receptor CXCR2 and the TGFβ signal redirection receptor, respectively.

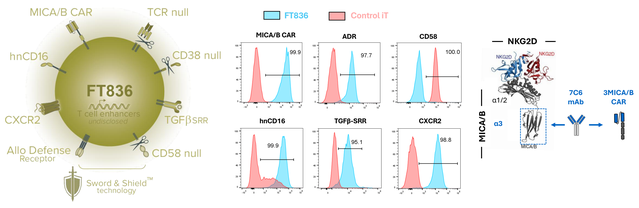
iPSC platform and multiplexed-engineering overcomes the challenges associated with existing approaches to cellular therapy

Platform Advantages

- ✓ **Defined Clonal MCB**: Single-cell derived, genetically uniform, selected for potency and genomic integrity.
- ✓ **Engineered MCB Starting Material**: One-time edit, highly scalable, donor-independent, and enables consistent high-quality products.
- ✓ **Modular Innovation**: Accelerates development through efficient, multiplexed engineering.

iPSC-derived Cell Therapy Products

- ✓ **Reliable, Scalable Drug Product**: Consistent, well-characterized, >5-year shelf stability; ~50,000-dose GMP-scale capacity at current site.
- ✓ **Cost-Effective & Consistent**: Low COGs (~$3,000/dose), inventory-based economics, and no donor variability.
- ✓ **Patient-Centered Therapy**: Off-the-shelf, antibody-like treatment with repeat dosing, low toxicity, and outpatient-friendly administration.



Summary & Conclusions

FT836 is a next generation, iPSC derived CAR T-cell uniquely designed for pan-tumor targeting of both solid tumors and hematological malignancies, engineered to eliminate the need for conditioning chemotherapy

- ✓ **Pan-tumor targeting**: Unique recognition of highly conserved α3 domain of MICA/B; synergistic with standard of care treatments (*e.g.* IMIDs, radiotherapy, and chemotherapy).
- ✓ **Multi-Antigen targeting:** Engineered to express hnCD16 to enable ADCC when combined with therapeutic monoclonal antibodies to combat tumor heterogeneity and antigen escape.
- ✓ **Resistance to host immune cell-mediated rejection:** Sword & Shield™ technology consisting of CD58 knockout (CD58^{KO}) for immune **evasion** and alloimmune defense receptor (ADR) to **selectively eliminate** allogeneic immune responses.
- ✓ **Elimination of lymphodepleting preconditioning**: Sword & Shield (ADR and CD58^{KO}) dual-resistance strategy to avoid pre-conditioning chemotherapy and eliminate the toxicity risks of lymphodepletion.
- ✓ **Engineered for additional performance in solid tumor settings**: Enhanced trafficking to the tumor; enhanced persistence and resistance to immunosuppressive tumor microenvironment.
- ✓ **Off-the-shelf**: Manufactured from an iPSC master cell bank that is derived from a fully characterized and multiplex-engineered clonal iPSC line, delivering uniform expression of functional elements at a large scale to support on-demand delivery.

FT836 was awarded TRAN1 grant from CIRM in January of 2025 to support its clinical translation. Phase 1 Clinical trial for FT836 in solid tumors is open for enrollment (NCT07216105).

Results

Stress antigens MICA/B and tumor antigen CD38 are broadly expressed in multiple myeloma

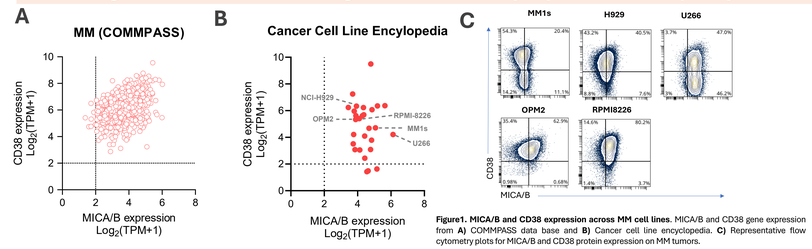


Figure1. MICA/B and CD38 expression across MM cell lines. MICA/B and CD38 gene expression from **A)** COMMPASS data base and **B)** Cancer cell line encyclopedia. **C)** Representative flow cytometry plots for MICA/B and CD38 protein expression on MM tumors.

FT836 exhibits potent cytotoxicity against MM by co-targeting MICA/B (CAR antigen) and CD38 (hnCD16 mediated ADCC) and mitigating the risk for antigen escape

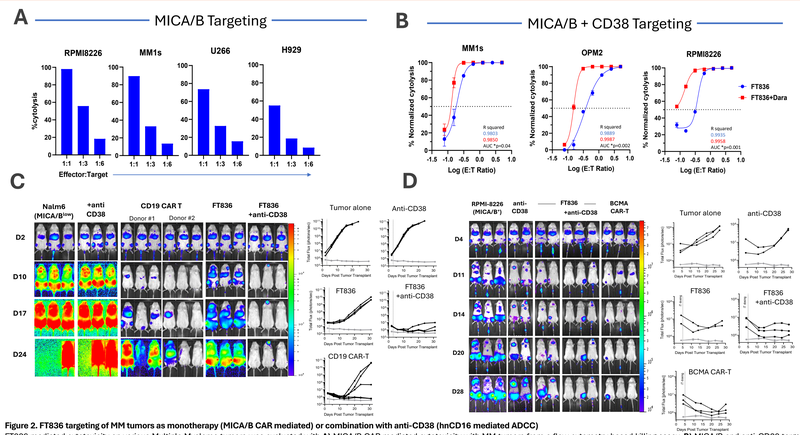


Figure 2. FT836 targeting of MM tumors as monotherapy (MICA/B CAR mediated) or combination with anti-CD38 (hnCD16 mediated ADCC)
FT836 mediated cytotoxicity on various Multiple Myeloma tumors was evaluated with **A)** MICA/B CAR mediated cytotoxicity with MM tumors from a flow cytometry based killing assay. **B)** MICA/B and anti-CD38 targeting of MM1s, OPM2 and RPMI8226 cell lines using luminescence based killing assay. In-vivo Stress model targeting of **C)** Nalm6 (MICA/B ^{low}) and **D)** RPMI8226 (MICA/B ^{high}) tumors by single dose (noted by vertical dashed line) of FT836 as monotherapy and/or combination with anti-CD38 treatment (Daratumumab). Nonlinear fit analysis was performed for luminescence-based cytotoxicity assay (B) and Unpaired t test was used for statistical analysis for AUC with/without daratumumab. *p=0.043, **p=0.0023 and ***p=0.001 for MM1s, OPM2 and RPMI8226, respectively.

SOC agents including IMIDs and radiation synergize with FT836 to enhance anti-tumor activity by upregulating stress antigens to induce deeper and more durable responses in MM

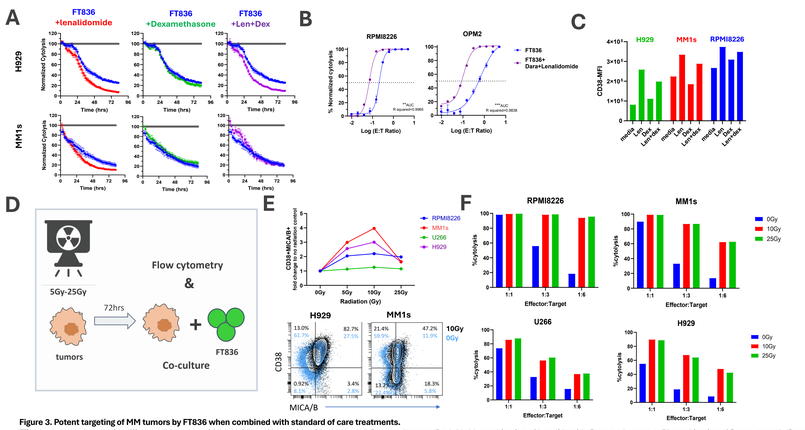


Figure 3. Potent targeting of MM tumors by FT836 when combined with standard of care treatments.
FT836 was co-cultured with different MM targets with and without **A)** Lenalidomide (Len) 1μM, Dexamethasone (Dex) 50nM, combination of Lenalidomide Dexamethasone or **B)** combination of Daratumumab (Dara) 1μg/ml plus Lenalidomide. **C)** Flow cytometry analysis of CD38 expression, MFI (Mean Fluorescence Intensity) on MM tumors post Lenalidomide, Dexamethasone or Len/Dex combination treatment. **D)** Schematic illustration of radiation. **E)** MM tumors received varying degree of radiation (5Gy to 25Gy). 72hrs post radiation MICA/B and CD38 expression was evaluated by Flow cytometry with two representative flow cytometry plots for CD38 and MICA/B expression changes post radiation. **F)** MICA/B targeting by FT836 was evaluated on MM targets 72hrs post radiation. Nonlinear fit analysis was performed for luminescence-based cytotoxicity assay (B) and Unpaired t test was used for statistical analysis for AUC with/without Len/Dara. **p=0.0012 and ***p=0.0009 for RPMI8226 and OPM2, respectively.

FT836 is engineered with Sword & Shield™ technology to support functional persistence in an allogeneic setting and eliminating the need for conditioning chemotherapy

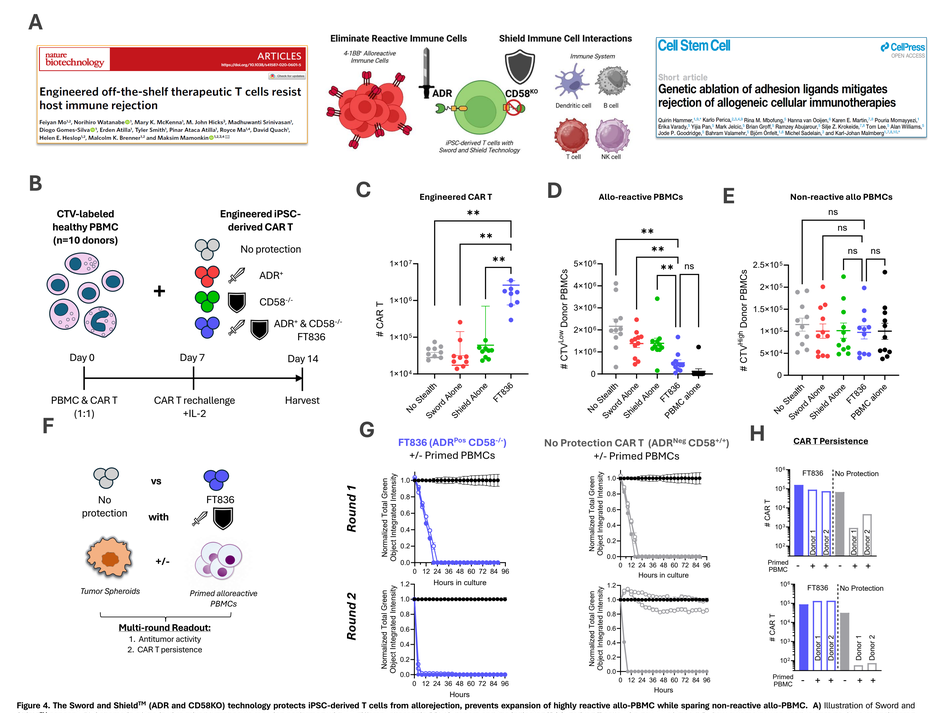


Figure 4. The Sword and Shield™ (ADR and CD58KO) technology protects iPSC-derived T cells from allorejection, prevents expansion of highly reactive allo-PBMC while sparing non-reactive allo-PBMC. A) Illustration of Sword and Shield™ concept. **B)** Schematic of the *in vitro* mixed lymphocyte reaction performed with 10 different allogeneic PBMC donors and the indicated iPSC-derived T cells. On day 14 of the MLR, flow cytometry was used to analyze **C)** total engineered CAR T cells remaining, **D)** total reactive allogeneic PBMC, and **E)** total non-reactive PBMCs. **F)** 3D Tri-cultures were set up to test the ability of Sword & Shield™ iT cells to resist primed alloreactive PBMC rejection in comparison to iT cells without Sword & Shield™ protection. **G)** FT836 mediated cytolysis of tumor spheroids was measured in a serial restimulation over two rounds of killing compared to no protection CAR T with/without primed PBMCs. **H)** Flow cytometric analysis of the indicated iT cells present at the end of each round. *One-way ANOVA, multiple comparison was used for statistical analysis of all graphs, showing indicated comparisons with *p<0.05, **p<0.001, ***p<0.0001, and ns = not significant.*

FT836 is engineered with CXCR2 to uniquely enhance trafficking to and residency in the TME

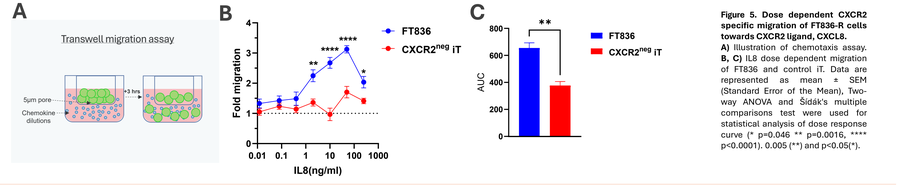


Figure 5. Dose dependent CXCR2 specific migration of FT836-R cells towards CXCR2 ligand, CXCL8.
A) Illustration of chemotaxis assay. **B, C)** IL8 dose dependent migration of FT836 and control iT. Data are represented as mean ± SEM (Standard Error of the Mean), Two-way ANOVA and Šídák's multiple comparisons test were used for statistical analysis of dose response curve (* p=0.046 ** p=0.0016, **** p<0.0001). 0.005 (**) and p<0.05(*).

FT836 exhibits potent persistence, and sustained function in an immuno-suppressive TME

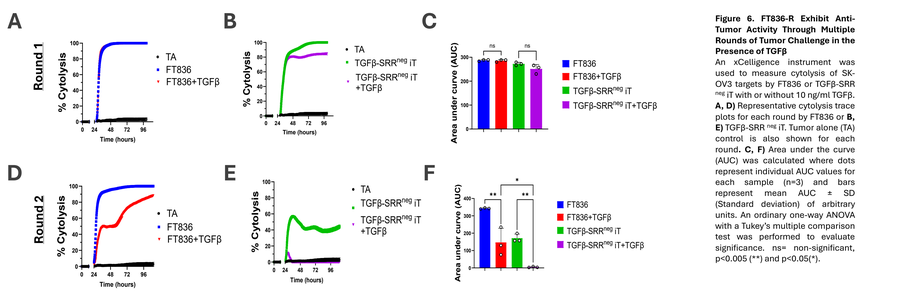


Figure 6. FT836-R Exhibit Anti-Tumor Activity Through Multiple Rounds of Tumor Challenge in the Presence of TGFβ
An xCelligence instrument was used to measure cytolysis of SK-OV3 targets by FT836 or TGFβ-SRR^{neg}iT with or without 10 ng/ml TGFβ. **A, D)** Representative cytolysis trace plots for each round by FT836 or **B, E)** TGFβ-SRR ^{neg}iT. Tumor alone (TA) control is also shown for each round. **C, F)** Area under the curve (AUC) was calculated where dots represent individual AUC values for each sample (n=3) and bars represent mean AUC ± SD (Standard deviation) of arbitrary units. An ordinary one-way ANOVA with a Tukey's multiple comparison test was performed to evaluate significance. ns= non-significant, p<0.005 (**) and p<0.05(*).