# FT576: Multi-specific Off-the-Shelf CAR-NK Cell Therapy Engineered for Enhanced Persistence, Avoidance of Self-Fratricide and Optimized mAb Combination Therapy to Prevent Antigenic Escape and Elicit a Deep and Durable Response in Multiple Myeloma

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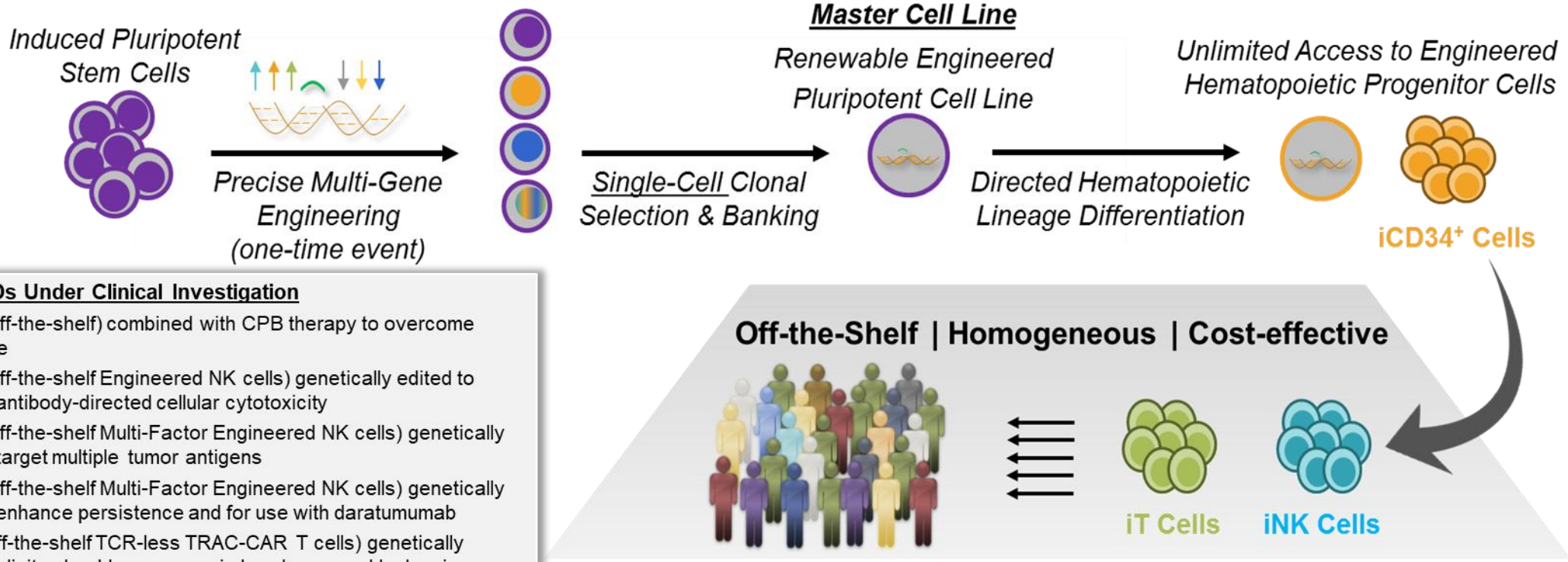
# Multiplexed Engineered iPSC-derived NK cell Platform for Off-the-Shelf Cancer Immunotherapy




**Cleared INDs Under Clinical Investigation**

- FT500 (Off-the-shelf) combined with CPB therapy to overcome resistance
- FT516 (Off-the-shelf Engineered NK cells) genetically edited to enhance antibody-directed cellular cytotoxicity
- FT596 (Off-the-shelf Multi-Factor Engineered NK cells) genetically edited to target multiple tumor antigens
- FT538 (Off-the-shelf Multi-Factor Engineered NK cells) genetically edited to enhance persistence and for use with daratumumab
- FT819 (off-the-shelf TCR-less TRAC-CAR T cells) genetically edited to elicit a durable response in lymphoma and leukemia

*Does not require patient-sourced cells*

*Eliminates stochastic editing variability associated with pool engineering*

*Consistent, reliable and cost-effective product forms*

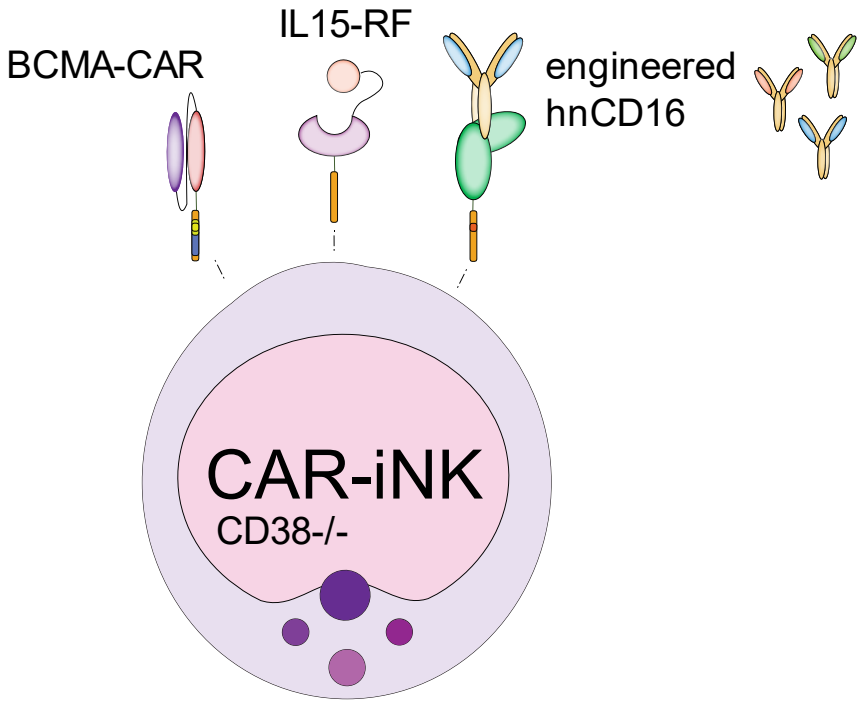
*Unprecedented scalability*

*Off-the-shelf production of cells*

***Addresses Critical Limitations of Patient- and Donor-Sourced Cellular Therapies***

# FT576 Translation of First-of-Kind Multi-Antigen Targeted Off-the-Shelf CAR-NK Cell with Engineered Persistence for the Treatment of Multiple Myeloma

**FT576: hnCD16 Fc Receptor ♦ BCMA-CAR ♦ IL-15RF ♦ CD38KO**

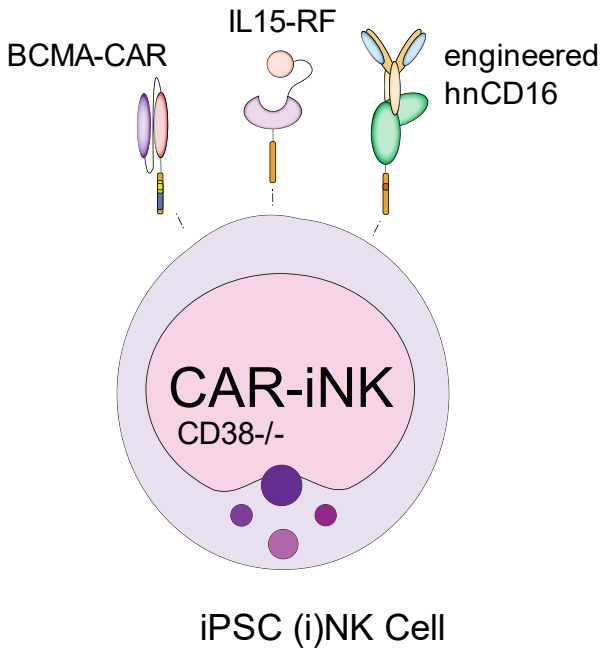



iPSC (i)NK Cell

**Precision Engineered Cell Product**

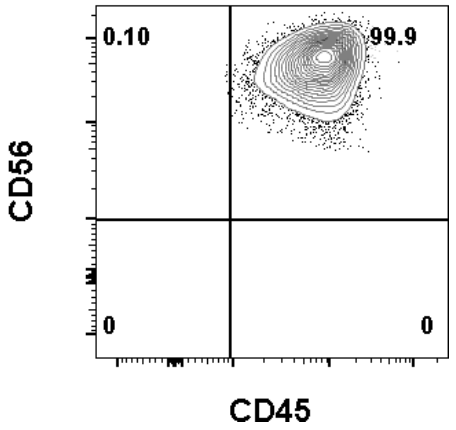
- ✓ Uniform NK cells derived from a multiplexed engineered clonal iPSC master cell bank developed to target myeloma
- ✓ Off-the-shelf availability through a renewable and highly scalable manufacturing process
- ✓ Potent multi-antigen targeting capability to prevent antigen escape
- ✓ Engineered for enhanced persistence
- ✓ Engineered to avoid fratricide in the presence of anti-CD38 mAbs
- ✓ Novel BCMA binder with increased antigen affinity (Bluhm et al. Molecular Therapy 2018).

# FT576 is an off-the-shelf NK cell product uniformly consist of four engineered anti-tumor modalities and is derived from a renewable clonal iPSC master cell bank



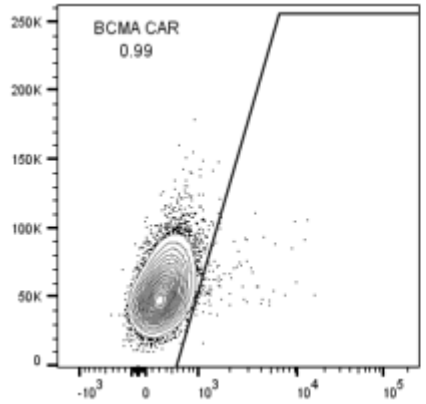

iPSC (i)NK Cell

## Uniform NK cell population

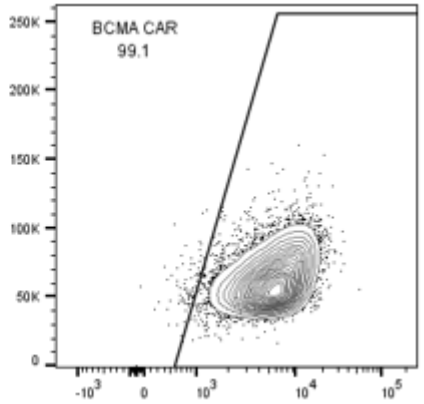



## Uniform CAR Expression

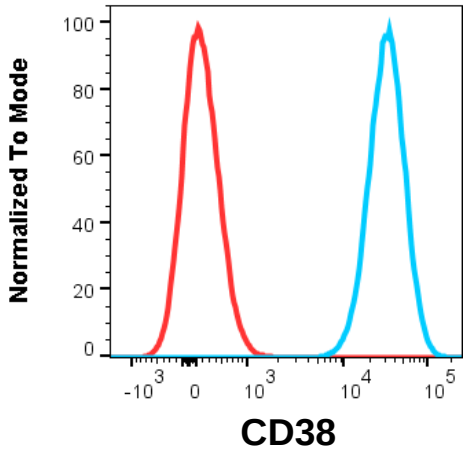
CAR negative NK cell

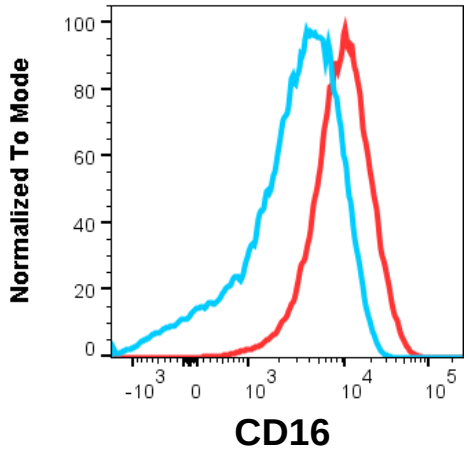


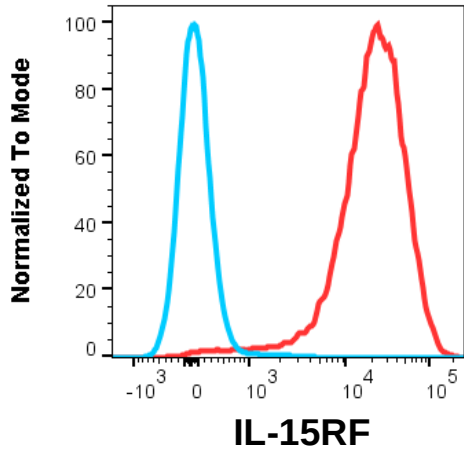

FT576




## Uniform Edited Modalities



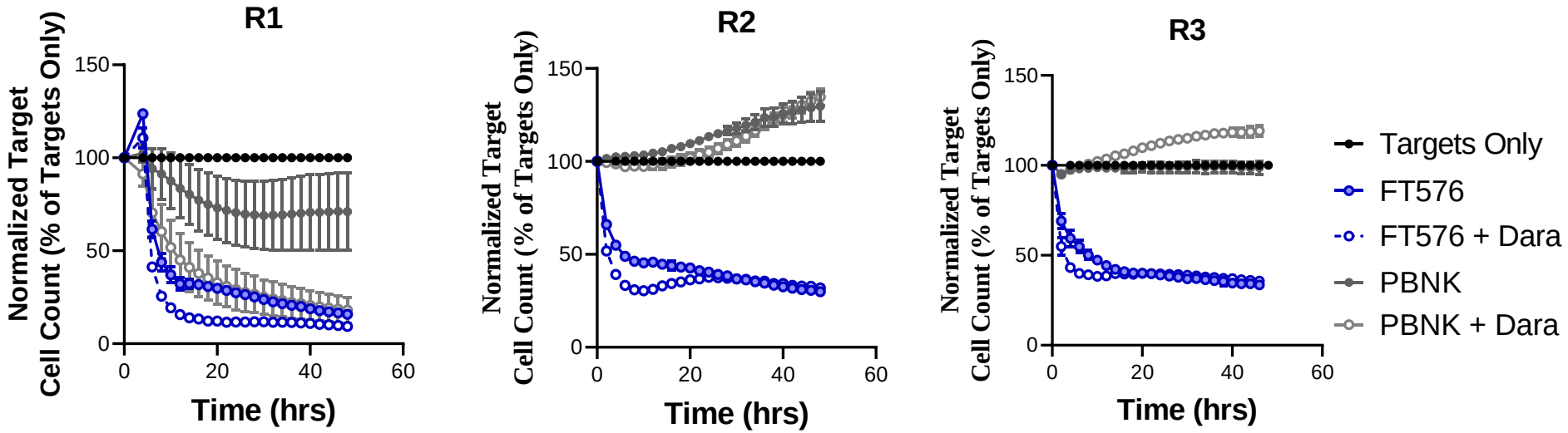




PBNK

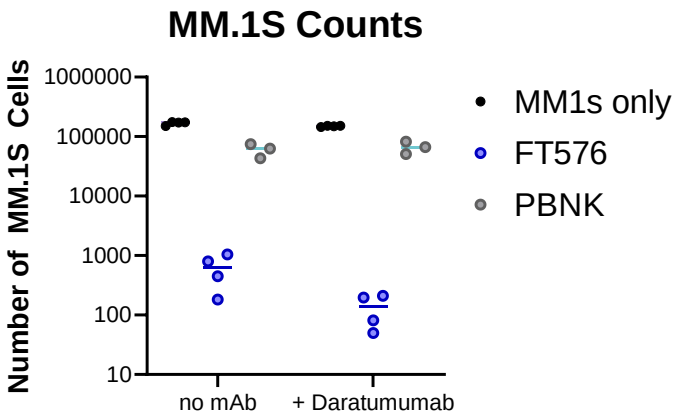
FT576

# FT576 demonstrates superior killing capacity and antigen-driven expansion while expanded PB NK cells fail to maintain anti-tumor response post first round of killing

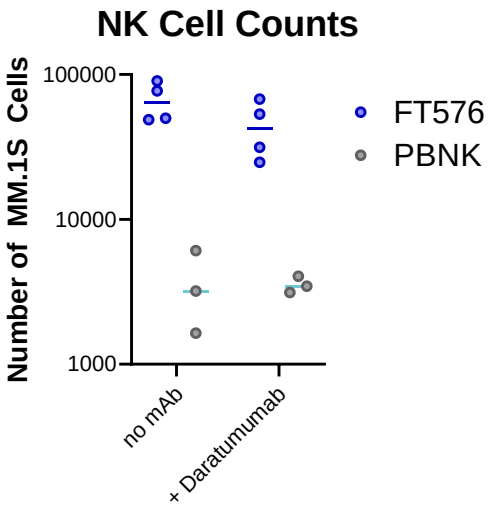
**A**




**B**




**C**

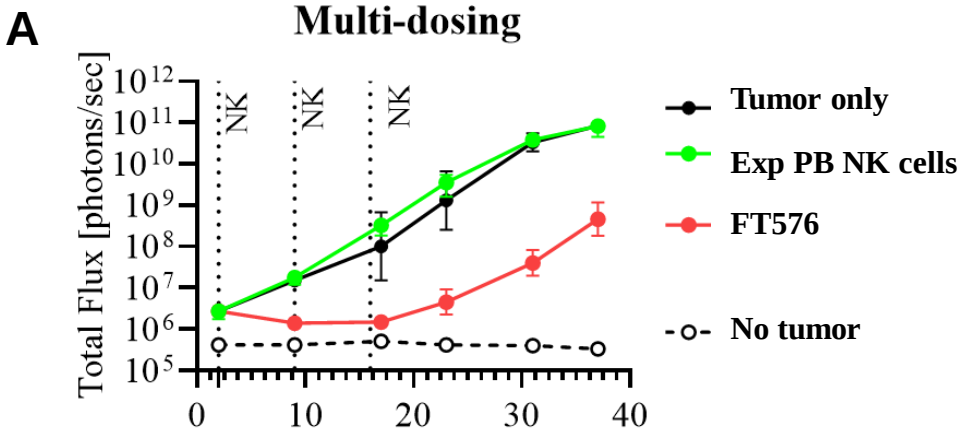


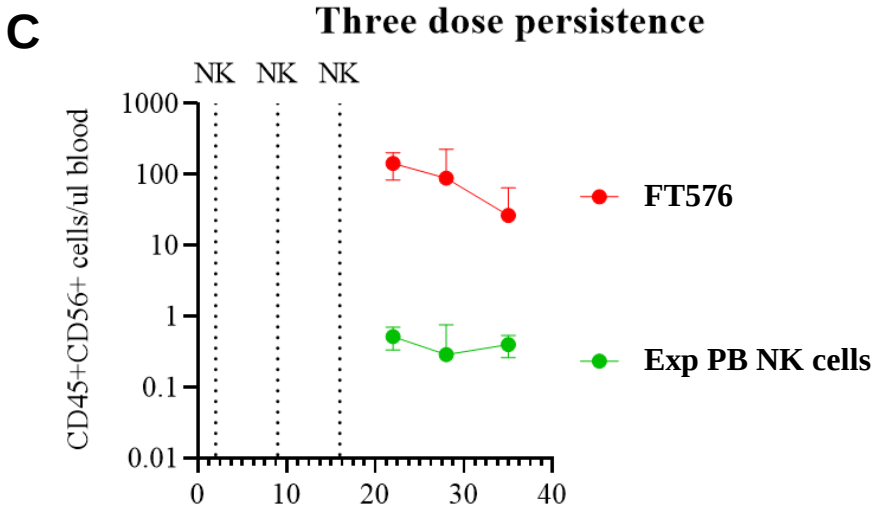

**Greater and More Persistent Cytotoxicity of FT576 vs Expanded PB NK Cells in an Incucyte Restimulation Assay.**

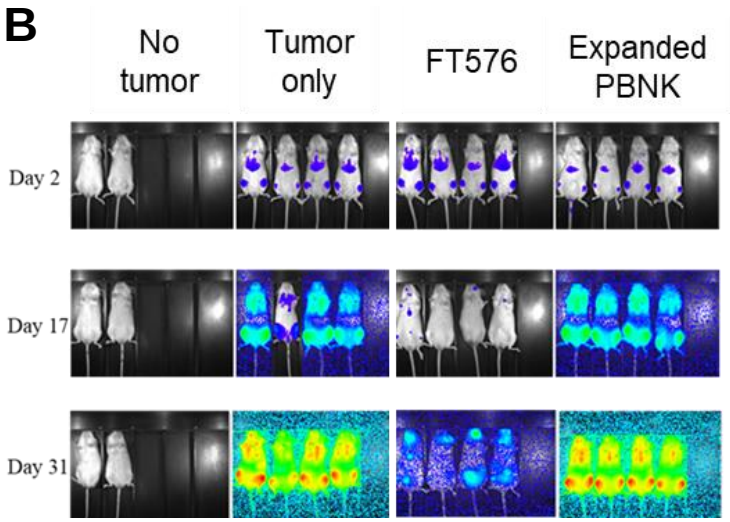
A serial restimulation cytotoxicity assay was performed against MM.1S cells in the presence and in the absence of daratumumab, using four independent batches of FT576 cells and expanded PB NK from three donors at a 10:1 E:T ratio.

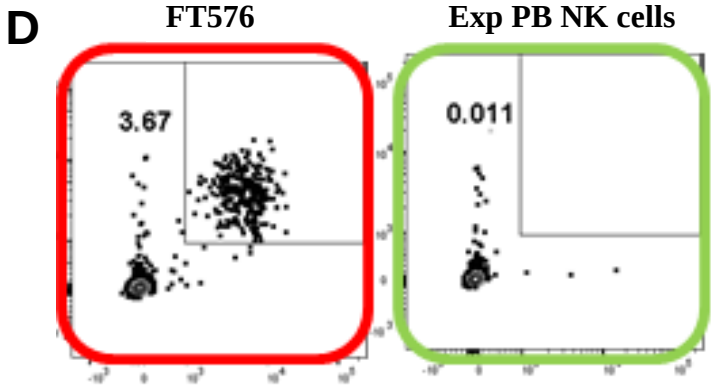
Cytotoxicity againt MM.1S was assessed by (A) Incucyte imaging in three consecutive rounds of stimulation (R1, R2, R3), and the number of (B) MM.1S cells or (C) NK cells present at the end of round 3 was assessed by flow cytometry.

# FT576 demonstrates enhanced efficacy and persistence in a disseminated xenograft model of myeloma



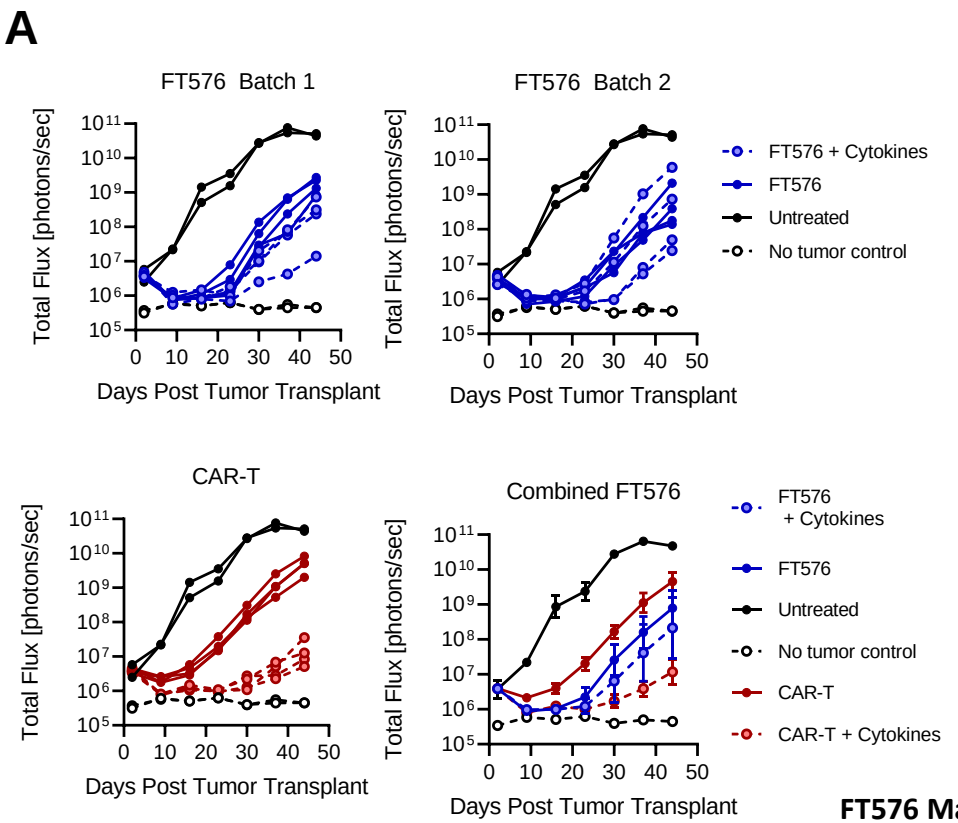



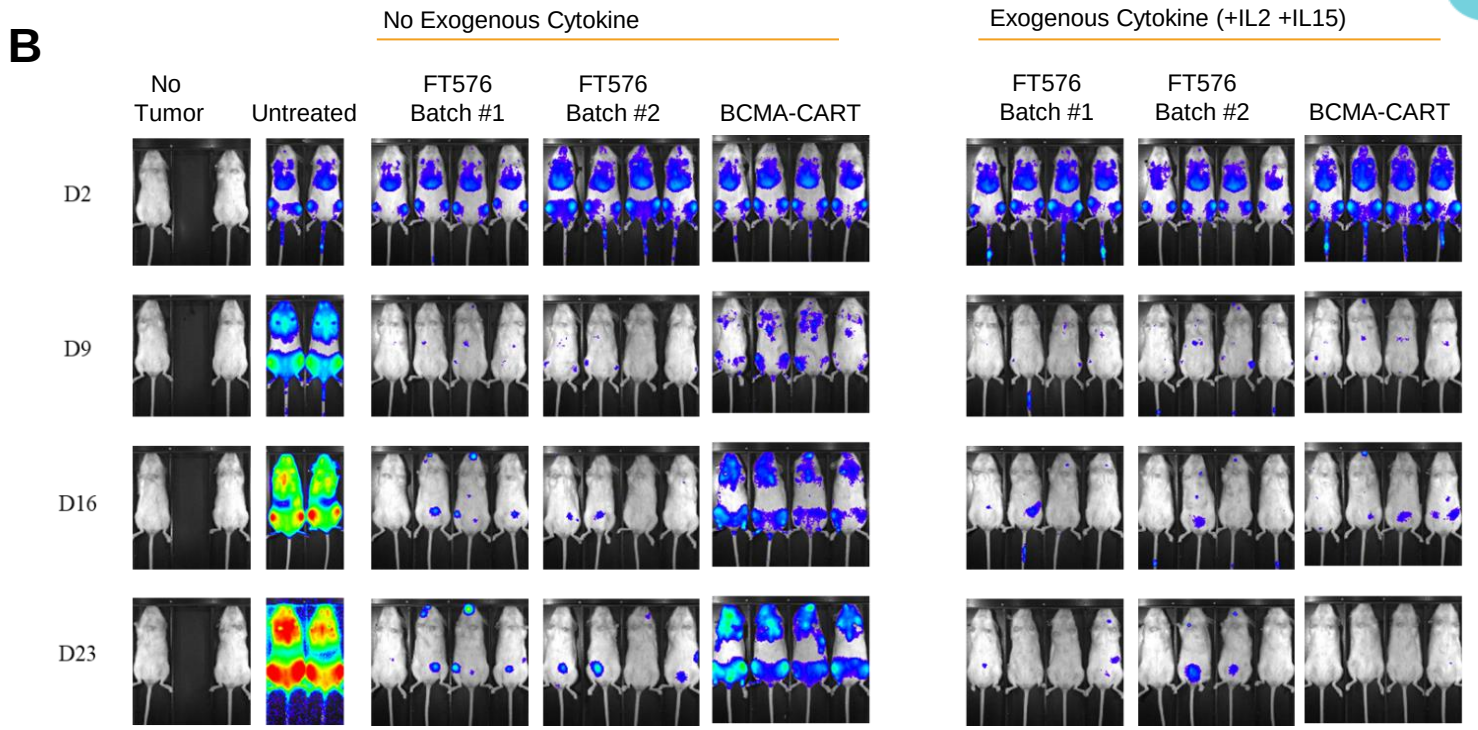




**In Vivo Efficacy and Persistence FT576 in Multi-dose Treatment Schedules.** IVIS imaging show greater control of MM1S tumor cells in mice treated with FT576 versus expanded pbNK (A and B) . NK cell persistence was assessed on DS22, DS28, and DS35 by flow cytometry of mouse peripheral blood(C) Representative dot plots are shown for the day 22 timepoint (D), and each plot is color-coded to the legend in panels (A) and (C).

# FT576 maintains similar efficacy to CAR T cells and does not require cytokine support

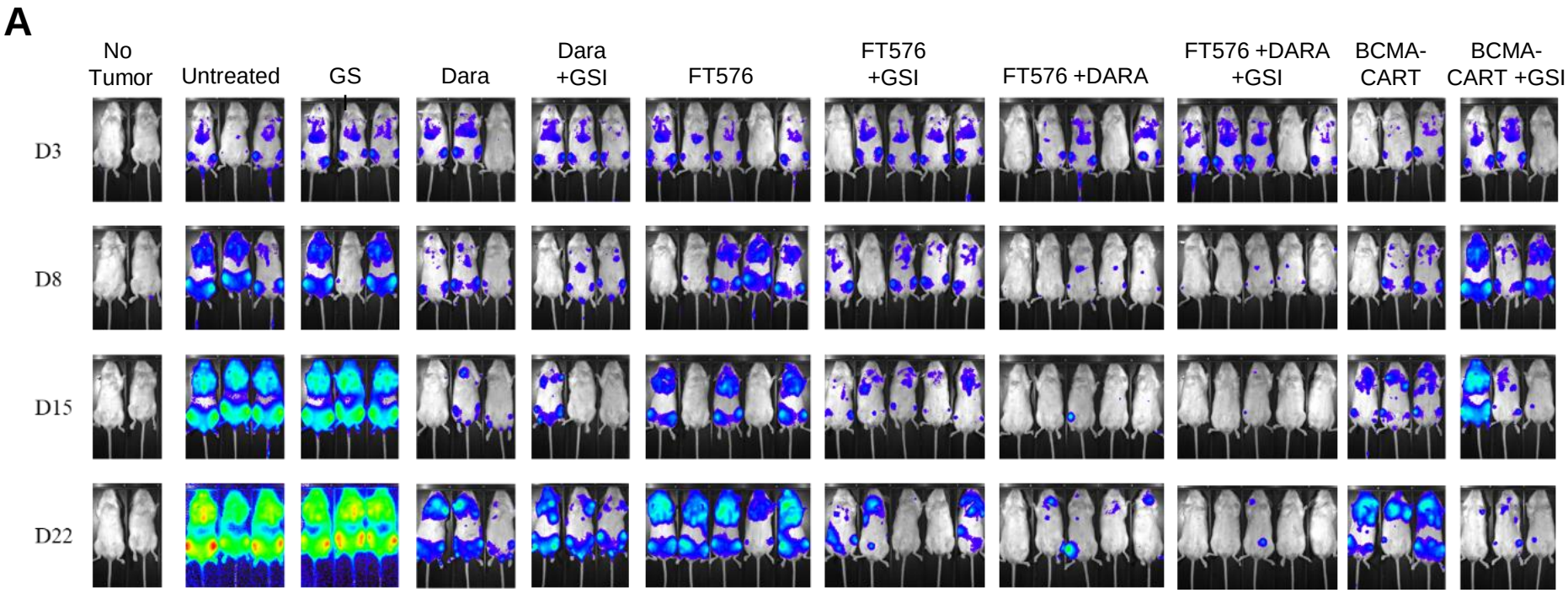


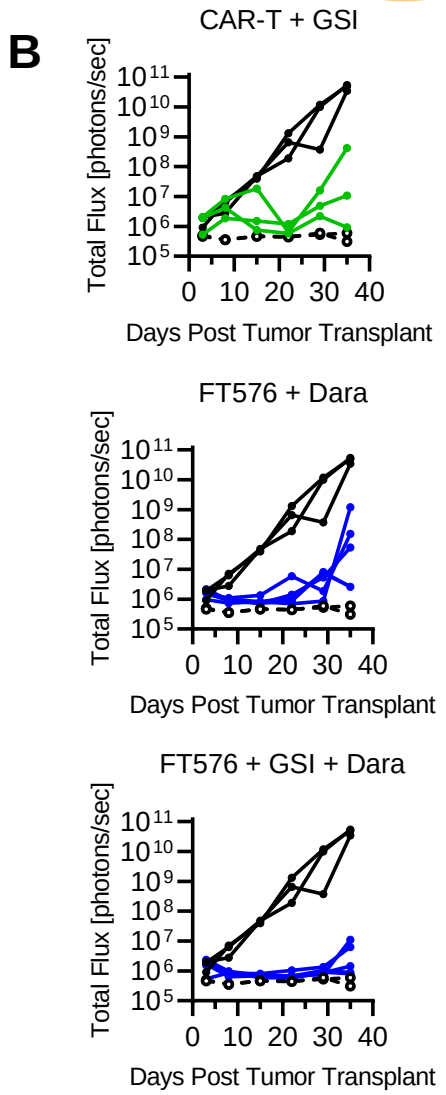




**FT576 Maintains In Vivo Efficacy in the Absence of Exogenous Cytokine Support**

NSG mice were transplanted with MM.1S-Luc cells and treated with 1E7 FT576 on DS2, DS9, and DS16, or treated with 2E6 primary CAR-T cells on DS2. Two batches of FT576 cells were used, and all three effector-treated groups were split and either left without additional cytokine support or were supplemented with twice-weekly injections of IL-15 and IL-2.
The data are presented as the BLI readings from individual mice for FT576 batch 1, FTiM0182 batch 2, and primary CAR-T cells, or the combined data (geometric mean ± geometric SD) from all FT576 treated mice in comparison to the CAR-T treated groups (A) BLI images are shown for each group (B)

# FT576 is highly synergistic with combinational treatment strategies including co-treatment with daratumumab




**Increasing BCMA Antigen Density with GSI Enhances FT576 In Vivo Function.**
Mice were dosed with GSI orally 2x/week for 3 weeks. BLI data for MM.1S-luc transplanted mice treated with three doses of 5E6 FT576 + GSI + Dara with additional single and combination therapy controls, including primary BCMA CAR-T (2E6 cells) BLI images for each mouse treatment group are shown (A) BLI levels over time for mice treated with CART and FT576 show that tumor clearance is improved by the addition of GSI (B)The negative control (no tumor) group is shown in the open symbols and dashed line on each plot.

# Summary

- To create a targeted cell therapy toward multiple myeloma with the aim to elicit a durable response, a unique multiplexed edited iPSC-derived off-the-shelf NK cell therapeutic, FT576, was created uniformly consisting of:
  - a proprietary CAR optimized for NK cell biology that targets BCMA
  - a novel high-affinity, non-cleavable CD16 (hnCD16) Fc receptor that enhances antibody-dependent cellular cytotoxicity (ADCC)
  - an IL-15 receptor fusion (IL-15RF) that augments NK cell activity
  - the deletion of the CD38 gene (CD38KO), which promotes persistence under oxidative stress and prevents NK cell fratricide in combination with CD38-targeted monoclonal antibody therapy
- The described studies demonstrate the versatility of FT576 as a highly effective multi-antigen targeting and cost-effective off-the-shelf BCMA-CAR NK cell product and supports the rational for a first-of-kind Phase I Study as a monotherapy or in combination with therapeutic mAbs targeted to MM-associated surface antigens, driving a path towards a curative therapeutic in MM

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