Phase 1 Translational Assessment of an Off-The-Shelf CAR NK Cell Armed with Alloimmune Defense Technology for Conditioning-free Therapy

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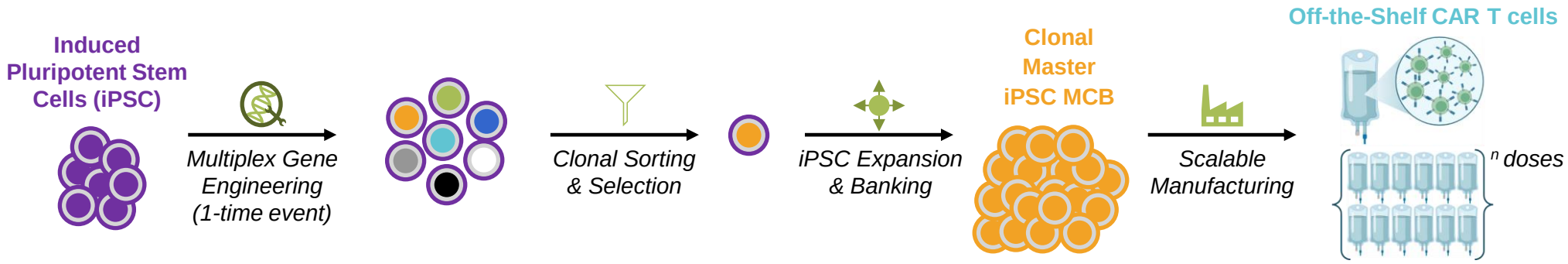
Off-the-Shelf Platform for Cell Therapy

Mass Produced, Multiplexed-engineered Cell Products for Off-the-shelf Patient Treatment



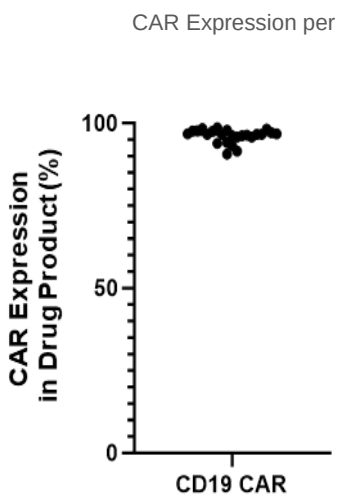
Platform Advantages:

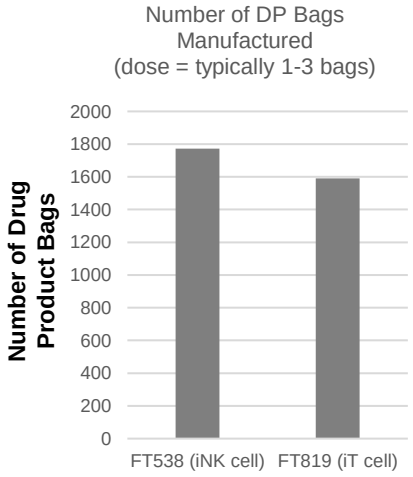
- ✓ Single-cell, CRISPR-based, multiplexed engineering
- ✓ Engineered master cell banks selected for genomic stability, differentiation capacity, and product functionality
- ✓ Highly-scalable, cost-effective GMP manufacture with no further engineering
- ✓ Fast, efficient and modular innovation

iPSC-derived Cell Therapy Products:

- ➢ Well-characterized, uniform in composition, consistent production of drug product
- ➢ Low cost of goods and not susceptible to donor-to-donor variability
- ➢ Monoclonal antibody-like treatment: on-demand availability, repeat dosing, ease of combinability
- ➢ Patient convenience and reach: off-the-shelf, reduced toxicities, reduced hospitalization, community setting

Uniform and consistent Inventory generated through routine manufacture





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iPSC Derived CAR Therapeutics

Top of the line scalability, homogeneity, and safety

Auto-CAR	Conventional Allogeneic CAR	iPSC CAR (off-the-shelf)
✓ Potent Targeted Therapy	✓ Potent Targeted Therapy	✓ Potent Targeted Therapy
✗ Requires Apheresis	✓ No Apheresis	✓ No Apheresis
✗ 2 Weeks of Engineering	✓ Pre-engineered	✓ Pre-engineered
✗ 7-10 Days Hospitalization	✗ 7-10 Days Hospitalization	✓ 0-3 Days Hospitalization
✗ Grade 3+ ICANS	✗ Grade 3+ ICANS	✓ No ICANS
✗ Limited Editing	✗ Limited Editing	✓ 10+ Edits (no upper limit)
✗ Variable Efficiency	✗ Heterogeneous and Inconsistent	✓ Homogenous and Consistent
✗ 1 Donor =1-2 Doses	✓ 1 Donor = 25-200 Doses	✓+ 1 MCB = ~10^9 Doses

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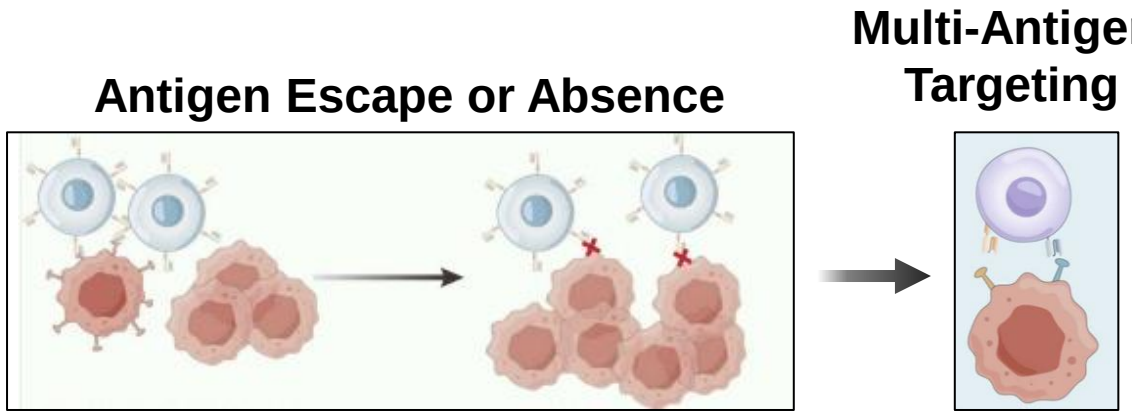
Product Design Considerations for FT522

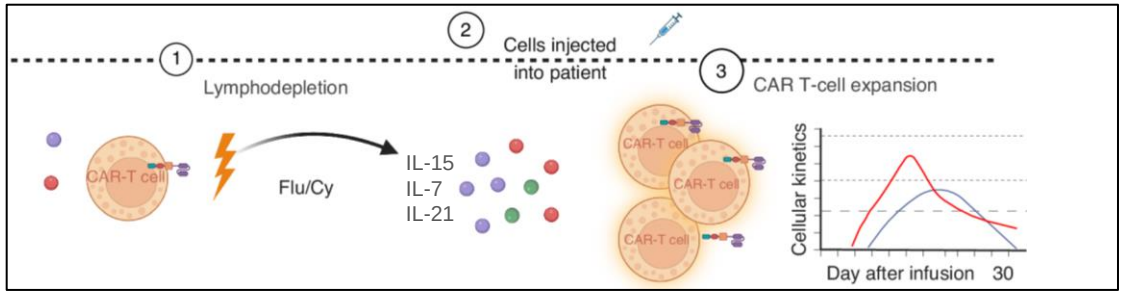
Uniquely promoting multi-antigen targeting and eliminating the need for conditioning chemotherapy

- **Flexibility to target multiple diseased cell types is needed to treat diverse, heterogenous and evolving hematological cancers**
  - Combination therapy is uniquely enabled to help cover multiple epitopes flexibly

- **Conditioning chemotherapy provides many factors that enhance cell therapy efficacy**
  - Provides reflexive cytokines essential growth factors and suppresses existing immune responses that may target product.
  - Induces cytopenia, increases susceptibility of severe infection and secondary malignancies, risks hospitalization, and limits patient access and reach.

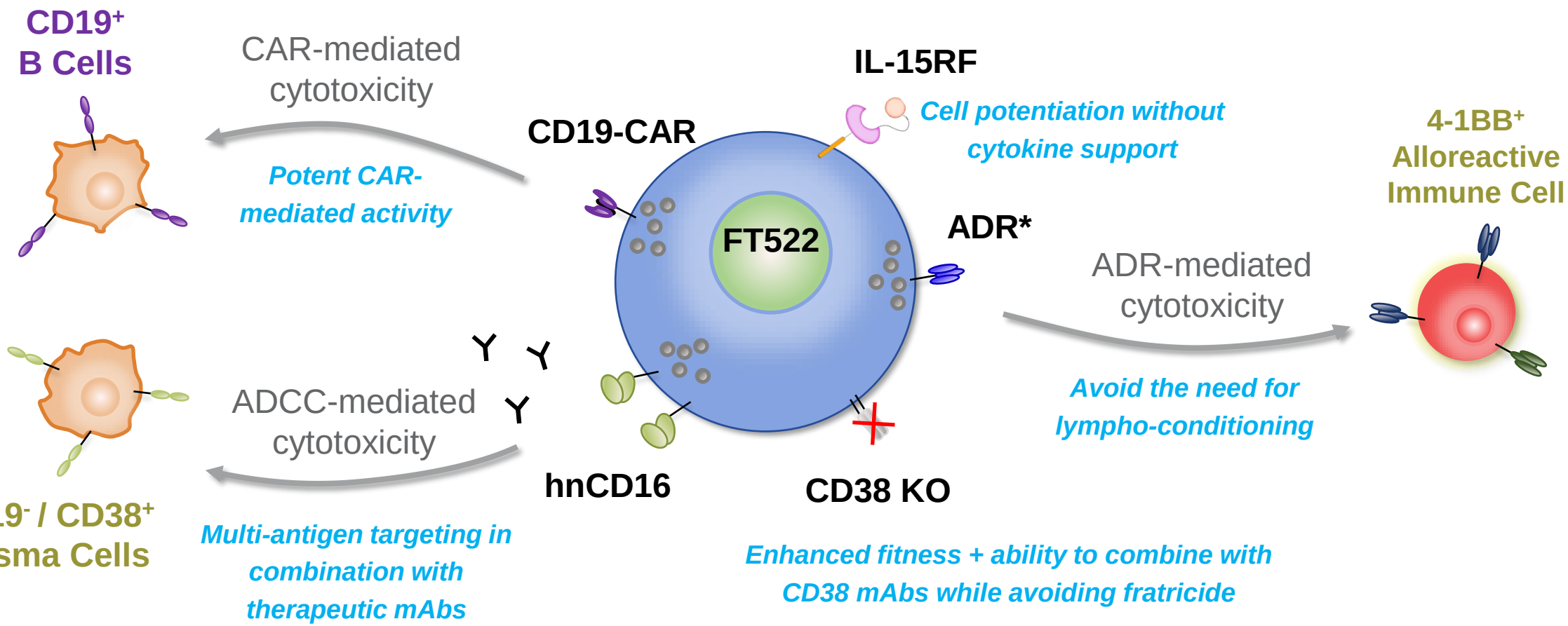


Adapted from Lin et al 2024 Biomed & Pharma



Adapted from Canelo-Vilaseca et al 2025 Bone Marrow Trans.

FT522: Next Generation Off-the-Shelf Multi-antigen Targeting CAR NK cell armed with ADR to Avoid the Need for Conditioning Chemotherapy

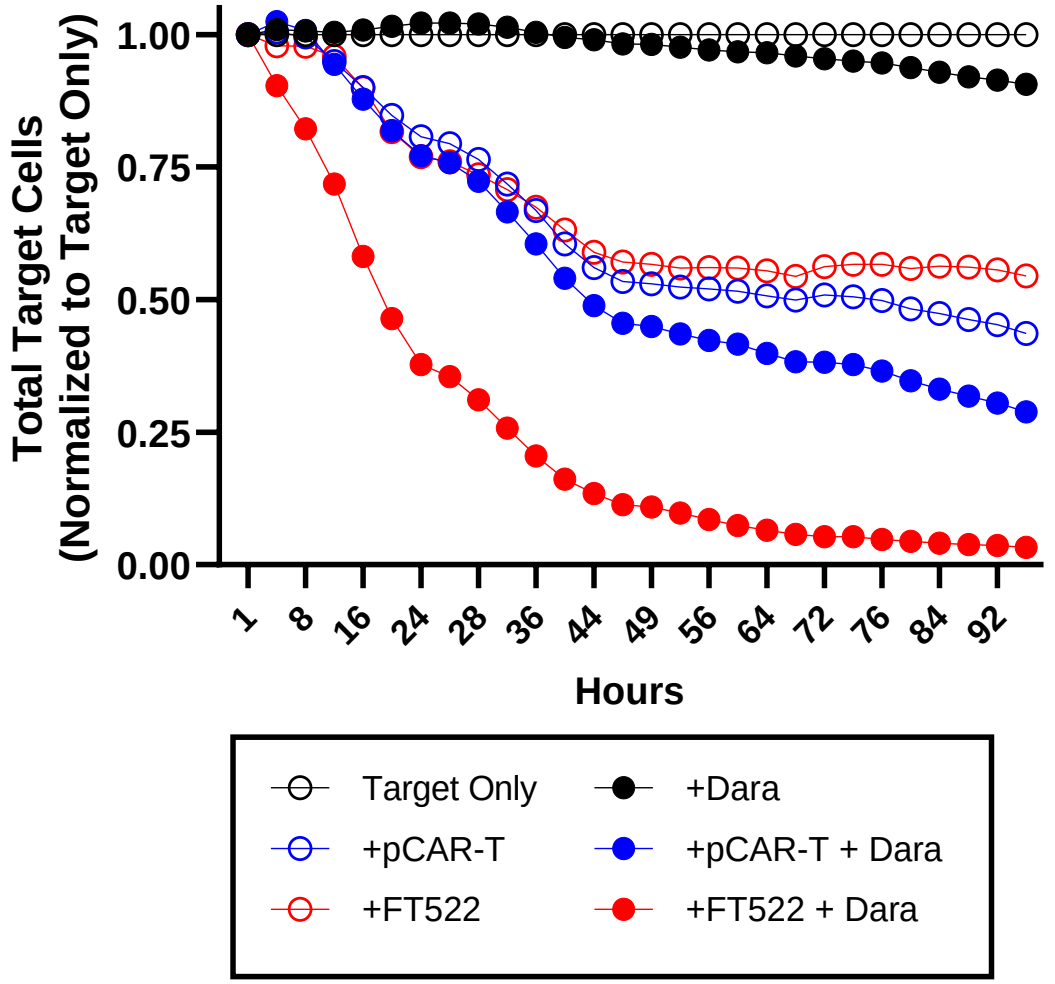


*Courtesy of Prof. M. Mamonkin, Baylor College of Medicine. Mo et al 2021 Nature Biotech

Multi-antigen Targeting of Diseased cells with mAbs Enhances Potency

Daratumumab and FT522 synergize for potent control of disease burden

- Design: 50/50 mixture of tumor line expressing CD19 & CD38 or CD38 alone
- Primary CAR-T or FT522 with CD19 CAR eliminate ~50% of Nalm/6
- CAR-T shows appreciable additive effect with Daratumumab
- FT522 exhibits pronounced synergistic increase in killing
- Similar enhanced activity seen with rituximab and other therapeutic mAbs



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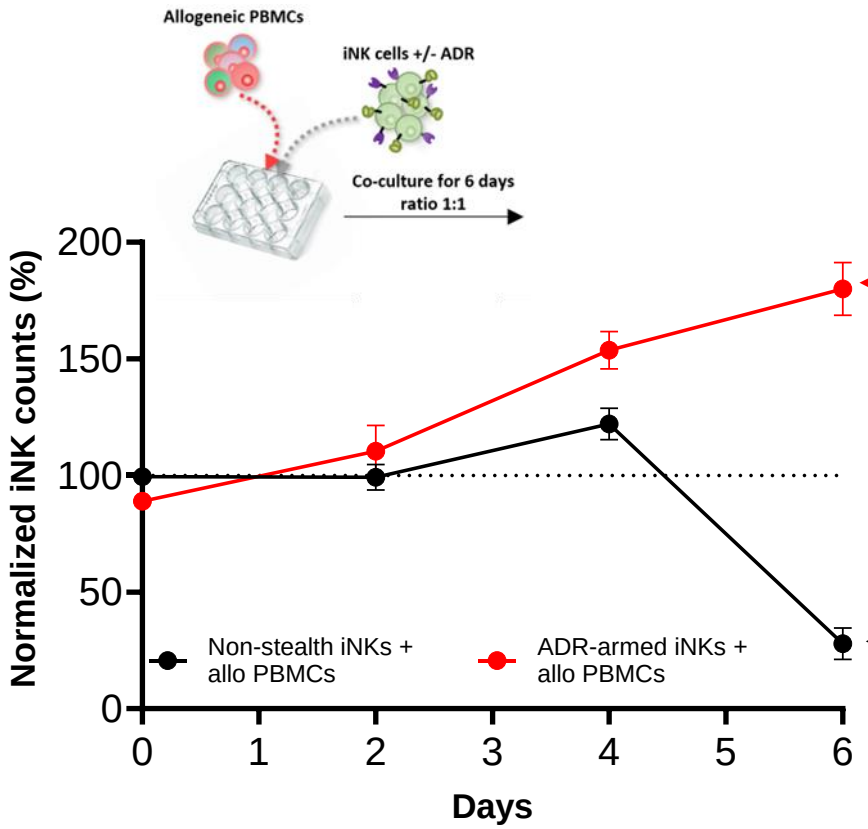
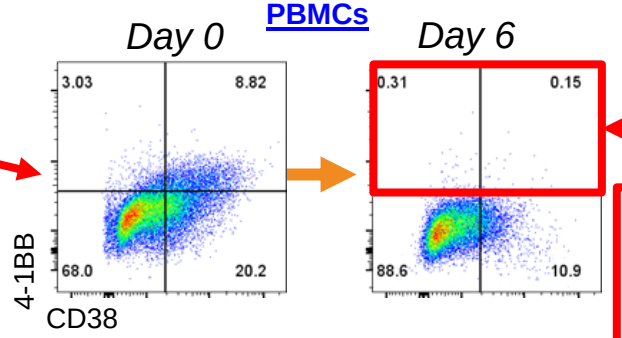
Allo-Defense Receptor Eliminates the Need for Conditioning Chemotherapy



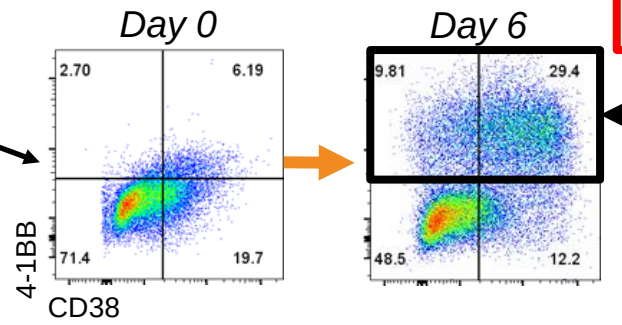
ADR-armed iNK cells
- Proliferate
- Eliminate alloreactive cells
- Persist

ADR-null iNK cells are eliminated in the presence of host PBMCs

ADR-armed iNK cells (FT522) + host PBMCs



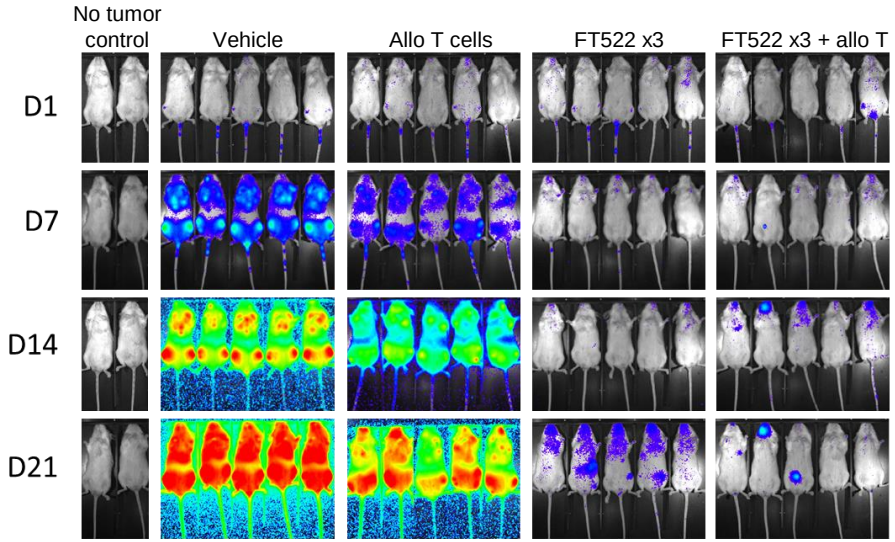
ADR-null iNK cells + host PBMCs

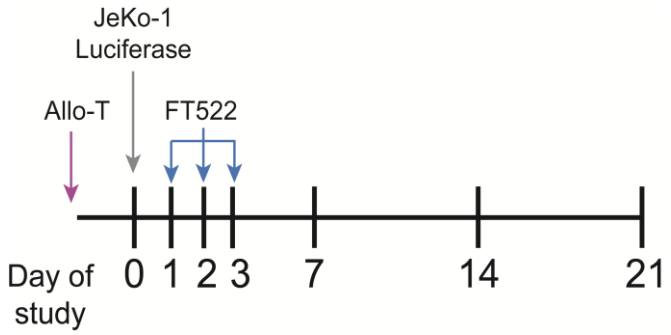


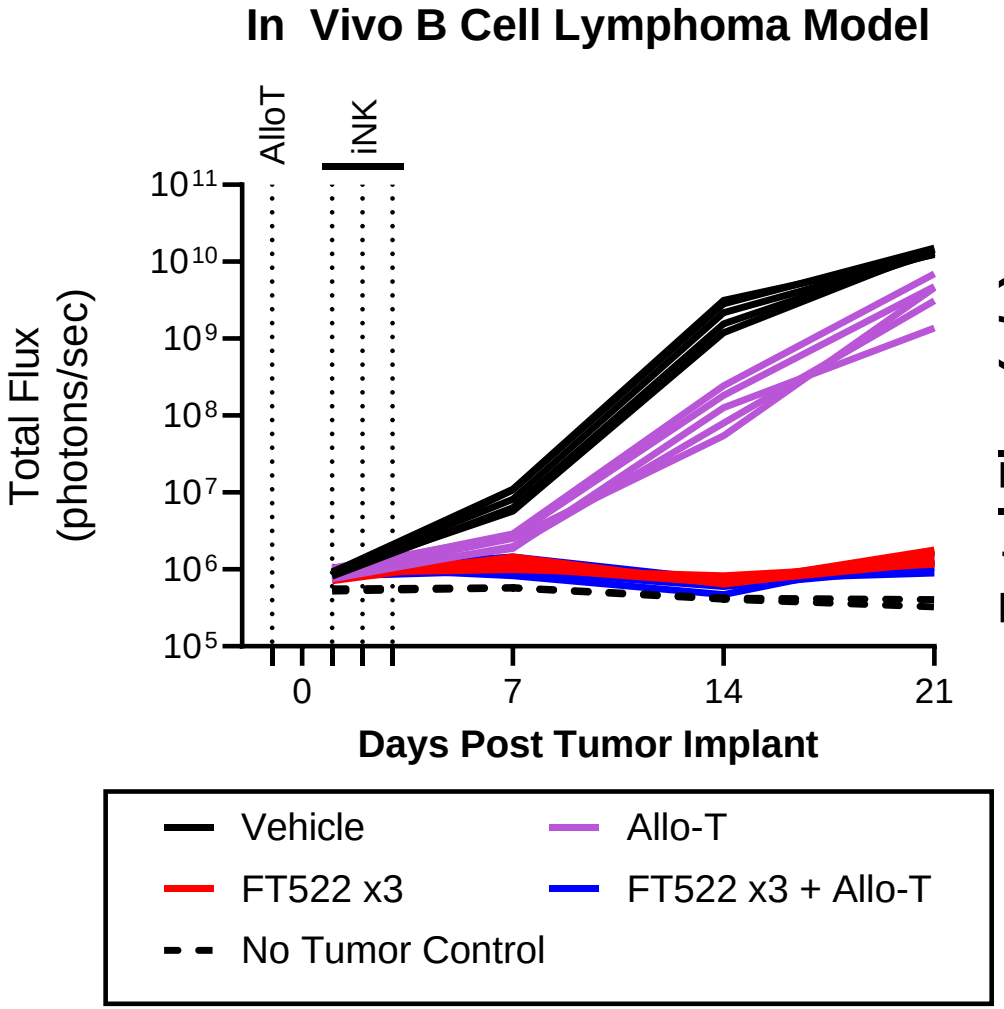
ADR-armed iNK cells eliminate alloreactive immune cells expressing 4-1BB.

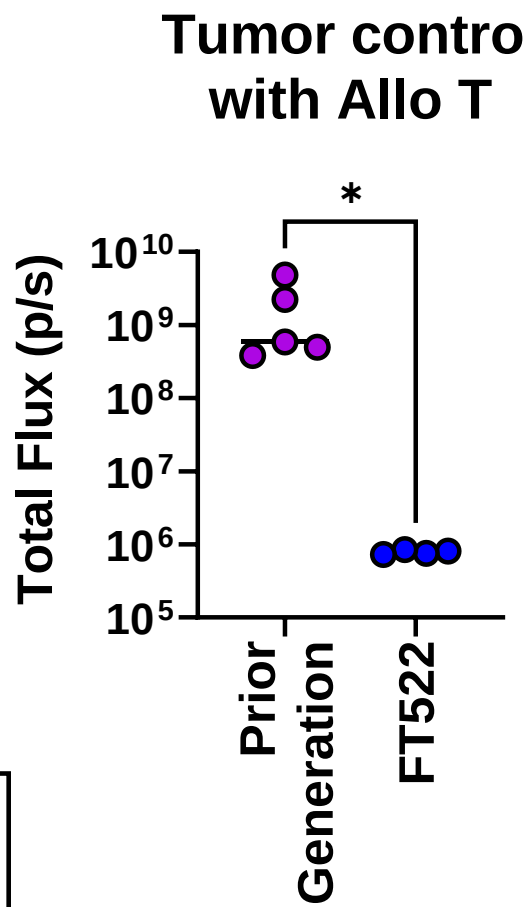
Enabling survival in an allogeneic system

FT522 Mediates CD19-Specific, Anti-Lymphoma Activity *in vivo* in the Presence of Highly Aggressive Primed Allogeneic T Cells







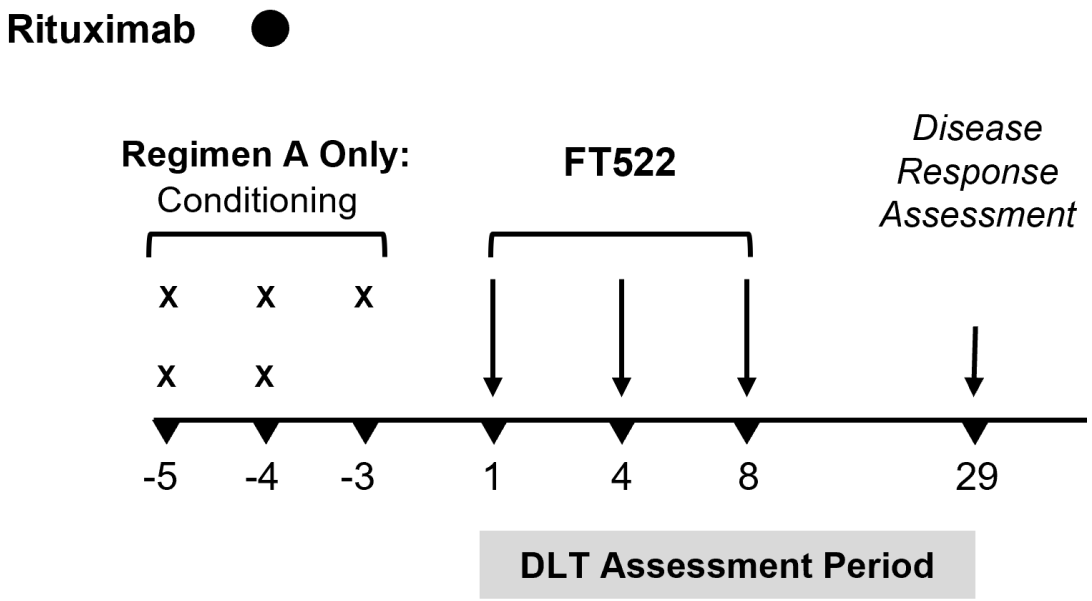


CAR, chimeric antigen receptor; CD, cluster of differentiation; MOA, mechanism of action.

Study Design for FT522-101

Evaluation of benefit without conditioning chemotherapy and efficacy of combination therapy

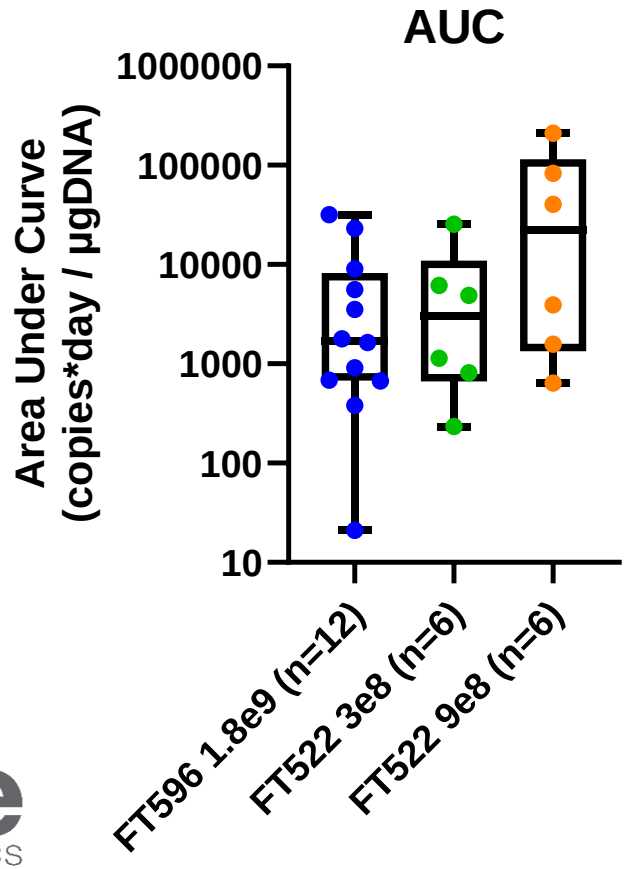
- Two Regimens (with/without Conditioning) in combination with Rituximab
- Three doses spaced 3 days apart
- Majority have prior exposure to Rituximab, indicating Rituximab is not sufficient for control of disease.
- Regimen A vs Regimen B allows comparison with/without conditioning chemotherapy.



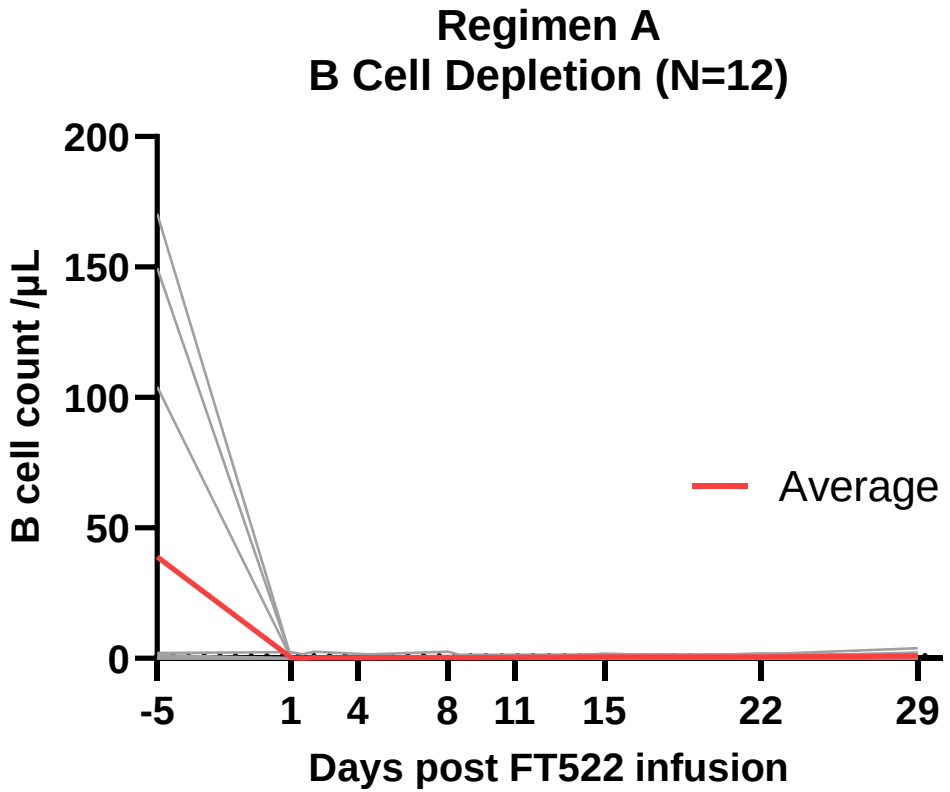
FT522 Persists and Associates with deep and lasting B Cell depletion

Improved Persistence Compared to Previous CAR-NK at lower doses

Improved Pharmacokinetics



Deep and Lasting B Cell Depletion

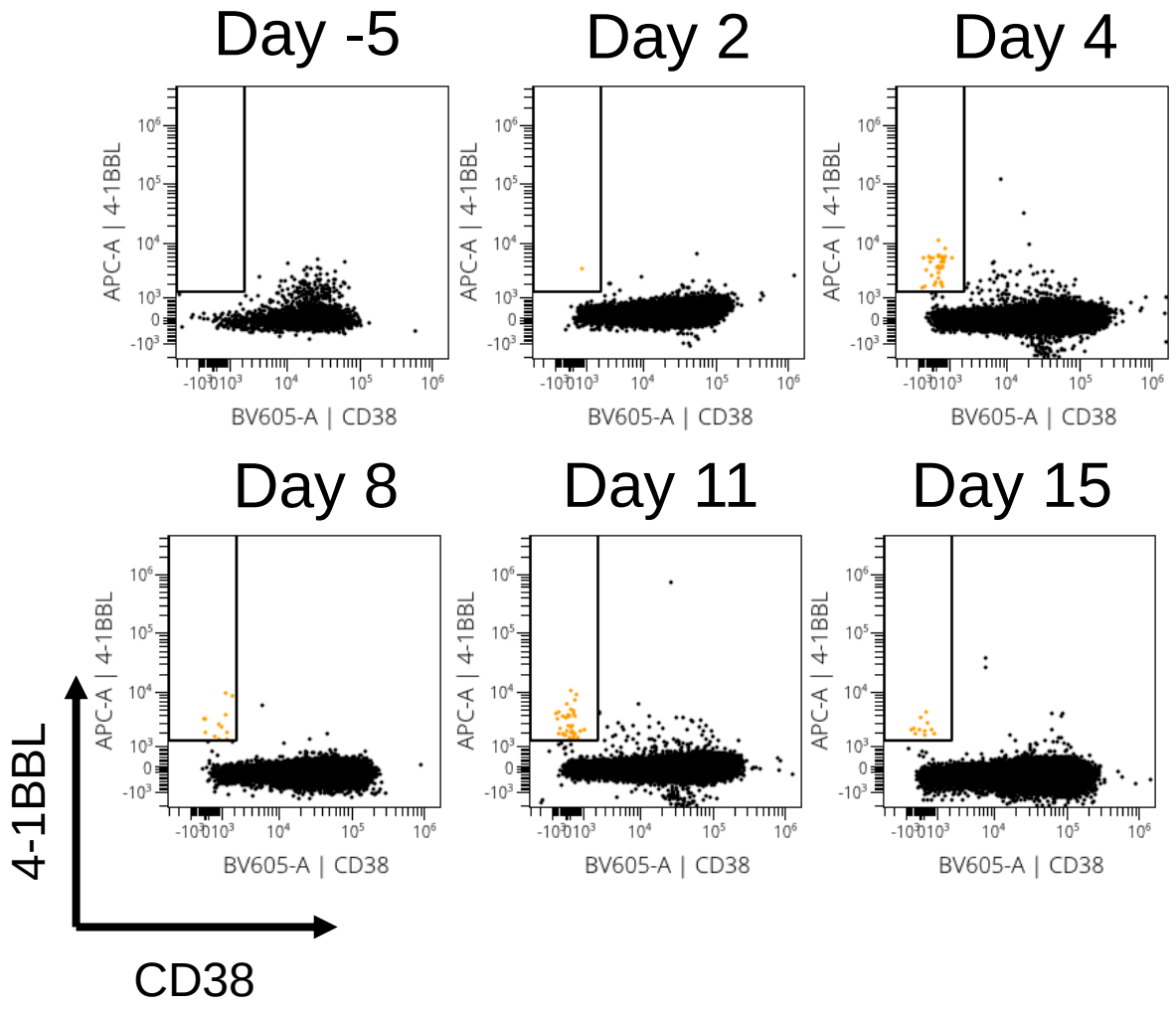


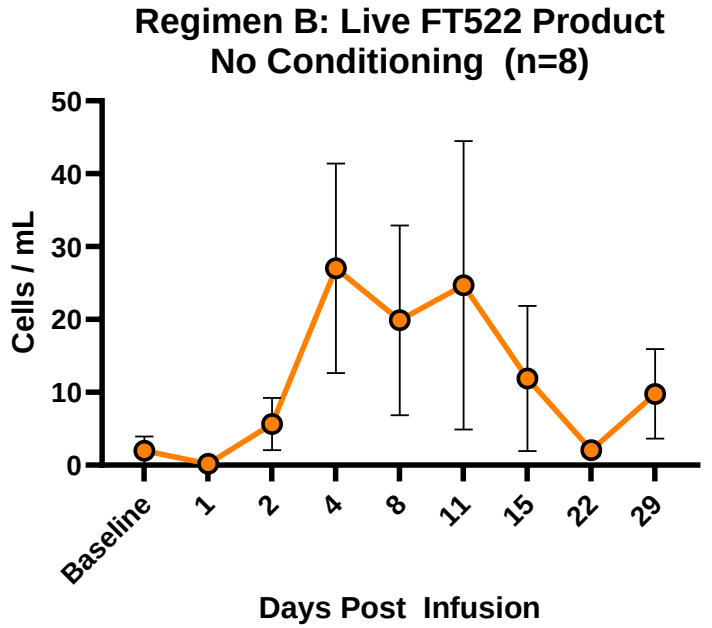
All data shown for Regimen A (with conditioning)

Case Study: Detection of FT522 by Flow Cytometry in Regimen B

Evidence for FT522 Survival and Persistence Without Cy/Flu

Long-Term Persistence Without Conditioning



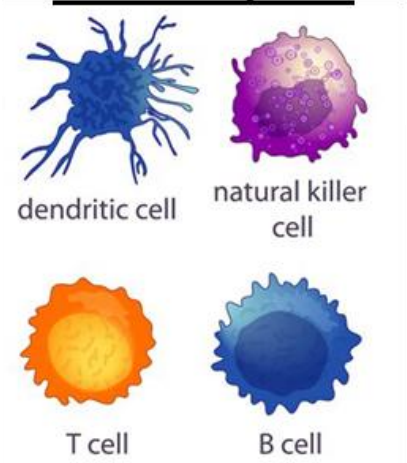


**No Patient to date shows cellular or humoral Anti-product responses*

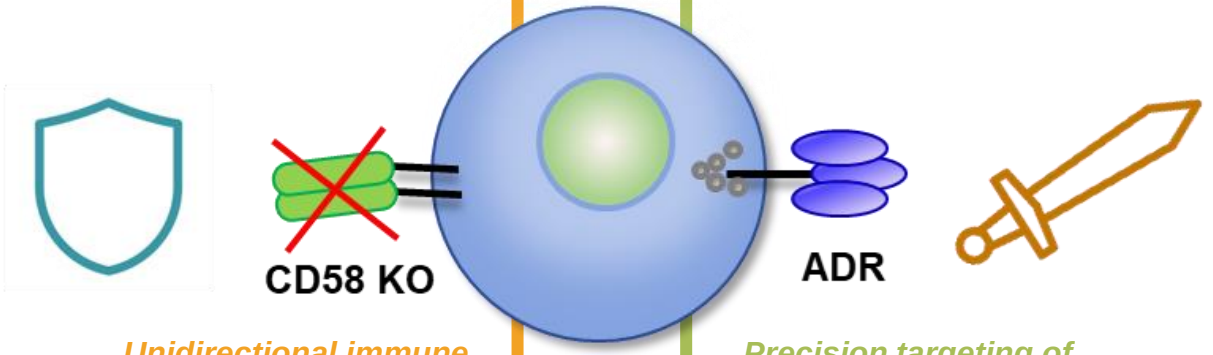
FT522 Provides the Bridge to Conditioning Free CAR Therapy for Next Generation CAR T cells

Pan-host Immune cell Evasion + Engagement with Alloreactive T cells to Protect and to Promote Potentiation

Immune System



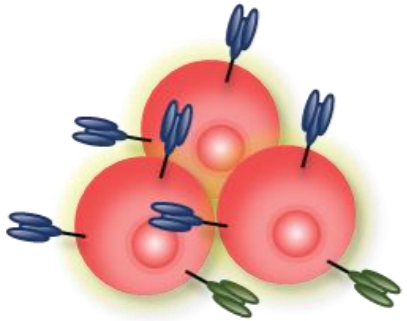
CAR iT/iNK cells



Unidirectional immune synapse disruption

Precision targeting of alloreactive immune cells

4-1BB⁺ Alloreactive Immune Cells



The Genetic Ablation of Adhesion Ligand CD58 Combined with Alloimmune Defense Receptor (ADR) is a Comprehensive Approach to Promote Functional Persistence of Allogeneic Cell Therapies without requiring CCT

Cell Stem Cell — CellPress OPEN ACCESS

Short article

Genetic ablation of adhesion ligands mitigates rejection of allogeneic cellular immunotherapies

Quirin Hammer, Karlo Perica, Rina M. Mbofung, Hanna van Ooijen, Karen E. Martin, Pouria Momayyezi, Erika Varady, Yijia Pan, Mark Jelcic, Brian Groff, Ramzey Abujarour, Silje Z. Krokeide, Tom Lee, Alan Williams, Jode P. Goodridge, Bahram Valamehr, Björn Önfelt, Michel Sadelain, and Karl-Johan Malmberg

nature biotechnology — ARTICLES

https://doi.org/10.1038/s41587-020-0601-5

Engineered off-the-shelf therapeutic T cells resist host immune rejection

Feiyan Mo, Norihiro Watanabe, Mary K. McKenna, M. John Hicks, Madhuwanti Srinivasan, Diogo Gomes-Silva, Erden Atilla, Tyler Smith, Pinar Ataca Atilla, Royce Ma, David Quach, Helen E. Heslop, Malcolm K. Brenner and Maksim Mamonkin

Summary and Conclusions

- FT522 is a next generation iPSC derived CAR-NK cell consisting of 5 genetic edits, uniquely made possible using iPSC platform
  - Cytokine Autonomy (IL15RF)
  - Synergistic Cooperation with CAR and mAb (hnCD16, CD38^{ko})
  - Self-protection against alloreaction (ADR)

- Detection of live FT522 during the treatment cycle **absent of chemotherapeutic conditioning** provides strong evidence that cells armed with ADR and cytokine autonomy **unique display functional persistence in patients**

- Next generation products will take advantage of, and build upon, these engineering advancements

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- Vaneet Sandhu
- Bob Valahmer
- Cindy Tahl

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