ML-Guided Epitope Steering and Antibody Optimization with Mammalian Display Generates a Diverse Panel of CD3 T-Cell Engagers

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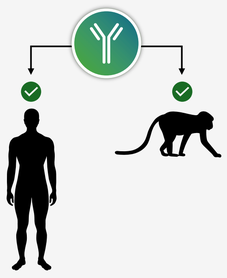
Key Challenges of CD3-Based T-cell Engagers

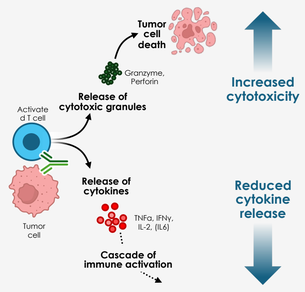
Developing T-cell engagers for use in cancer treatments can be challenging due to the strict efficacy and safety requirements for these antibody therapeutics. We solve this problem by discovering a sequence-diverse, cynomolgus monkey cross-reactive panel of T-cell engagers using a machine learning (ML) approach for epitope steering and optimization with a mammalian display platform. The resulting antibody panel spans a broad ~10^3 range of T-cell binding and activation. Finally, tumor-specific killing is demonstrated when the T-cell engagers are paired with tumor associated antigen arms in a bispecific format.

1 Sequence Diversity

2 Hu-Cyno Cross Reactivity

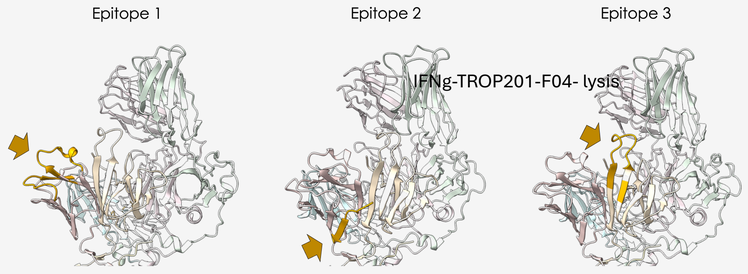


3 Range of Cyto-kine Release

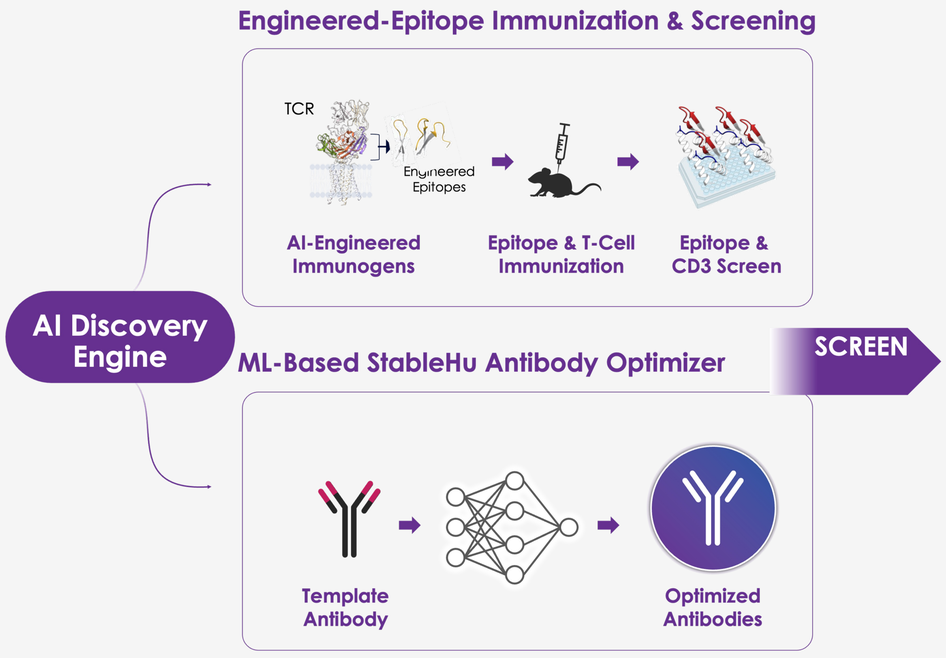


Our Solution

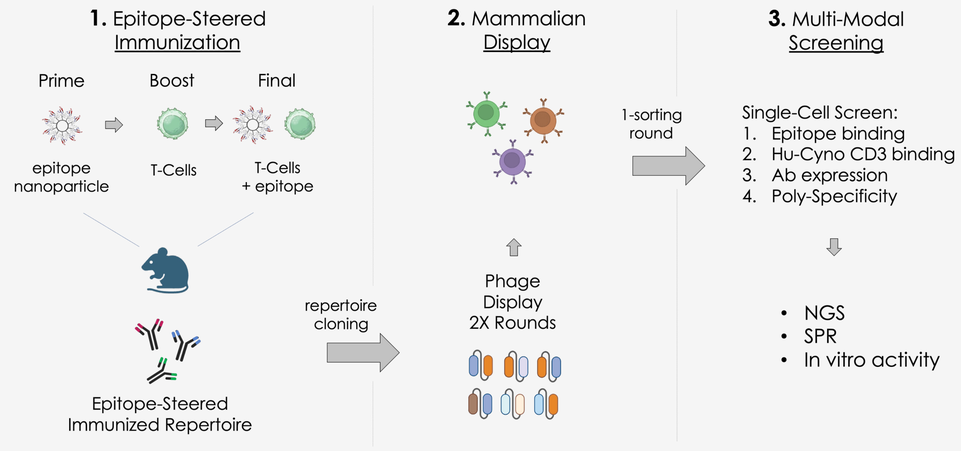
Selection of TCR Accessible & Human-Cyno Cross-Reactive Epitopes



Dual Approach to a Diverse Panel of Anti-CD3 Antibodies



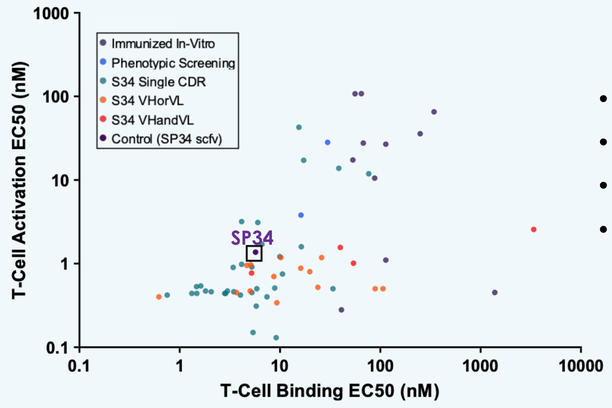
Multi-Dimensional Optimization of Clones with Mammalian Display



Pre-Clinical Validation

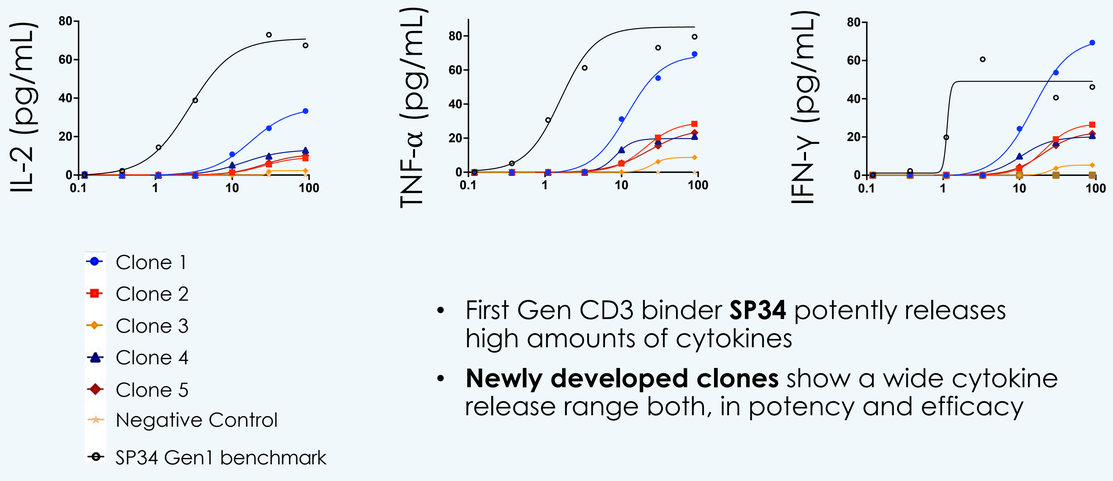
Highly Sequence-Diverse CD3 Panel

T-Cell Binding vs Activation



- **68** prioritized clones
- T-cell binding range **>1000x**
- T-cell activation range **>800x**
- Bispecifics tested on OVCAR-3 cells with primary human PBMCs

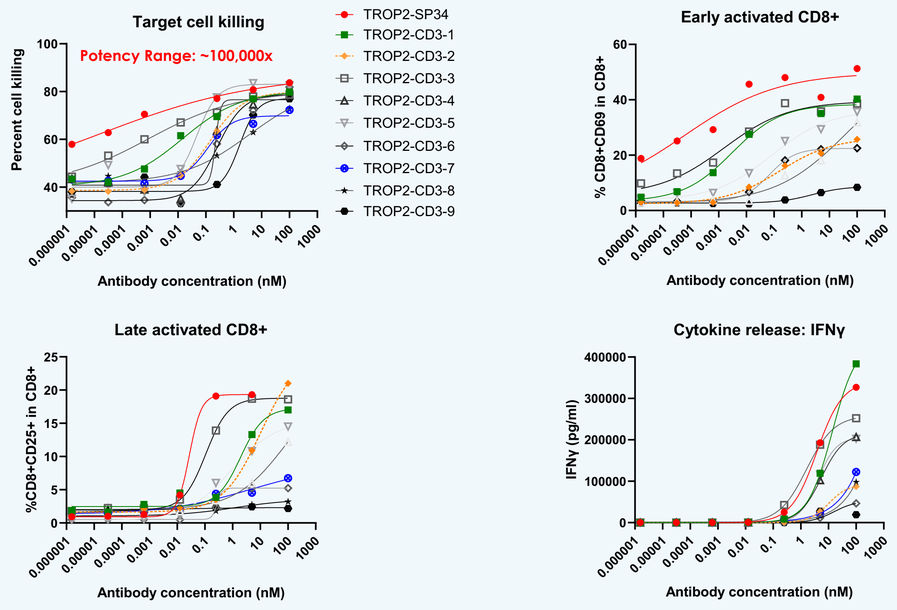
5 Selected Clones Show Wide Range of Cytokine Release



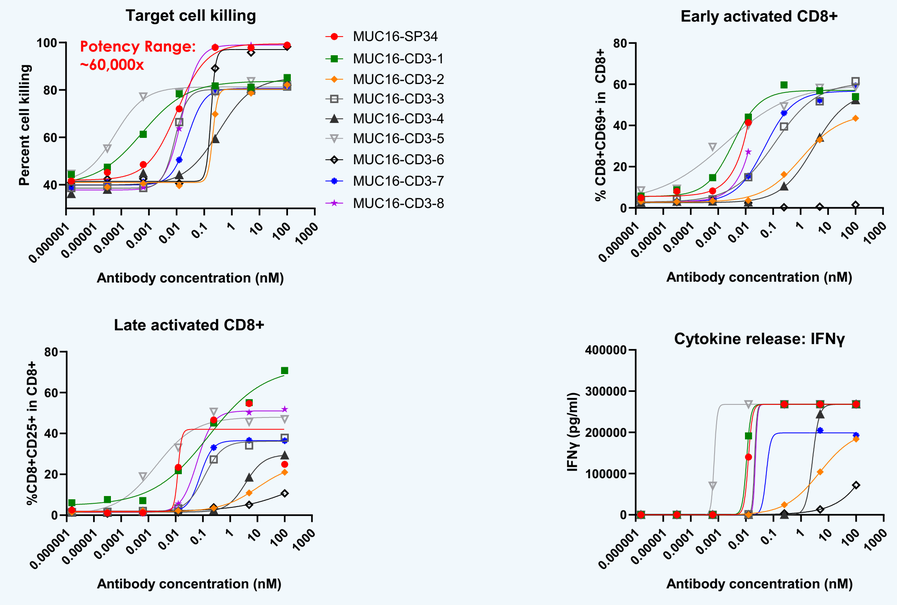
- First Gen CD3 binder **SP34** potently releases high amounts of cytokines
- **Newly developed clones** show a wide cytokine release range both, in potency and efficacy

CD3 Panel Creates TROP-2 and MUC16 Bi-specifics with Wide Cell-Killing Potency Range

TROP-2 Bispecifics Show Wide Potency Range of T-Cell Activation and Ovarian Cancer Cell Killing



MUC16 Bispecifics Show Wide Potency Range of T-Cell Activation and Ovarian Cancer Cell Killing



For cytokine release and tumor cell killing assays, human PBMCs and the ovarian cancer cell line Ovcar3, which expresses both TROP-2 and MUC16, were used to evaluate the activity of TROP-2 x CD3 and MUC16 x CD3 bispecific antibodies.