Generating potent and specific soluble TCR-based T cell engagers via a high-throughput yeast-based platform

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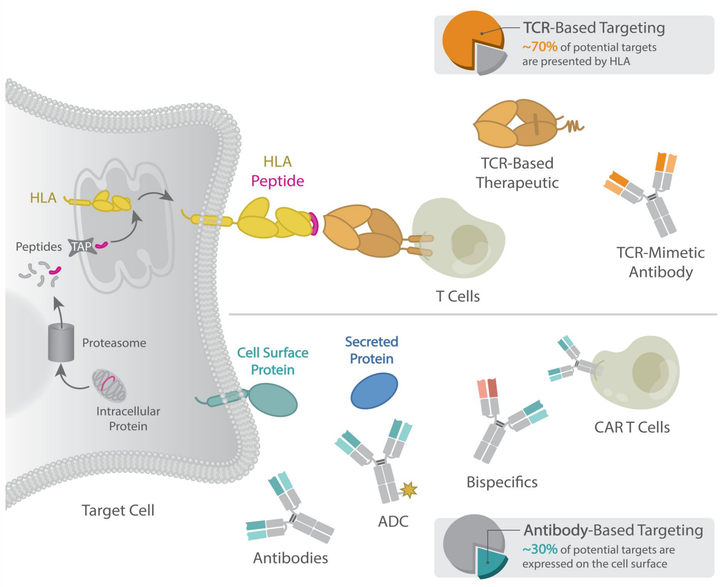
ADIMAB

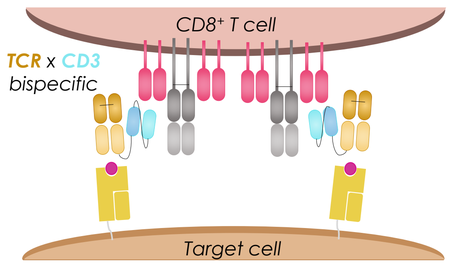
Background – Soluble TCR-based T cell engagers

pHLA-targeting therapeutics

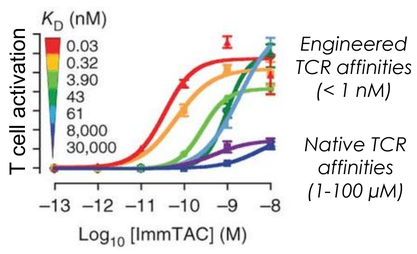


Cites data from Chandran, S.S. & Klebanoff, C.A. (2019) Immunol Rev

TCR-based T cell engagers



TCR affinity drives TCE activity

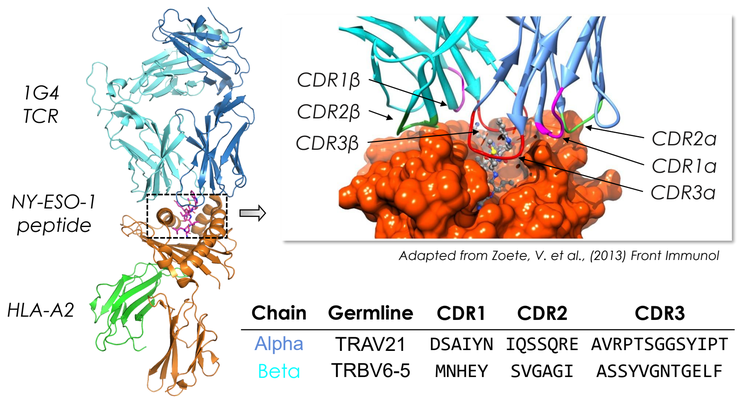


Adapted from Liddy, N. et al (2012) Nat Med

Soluble TCR-based T cell engagers enable potent and specific targeting of otherwise inaccessible intracellular antigens via peptide-HLA recognition and redirected T cell killing yet require extensive affinity maturation for function in clinically validated formats.

Background – Cancer-targeting 1G4 TCR

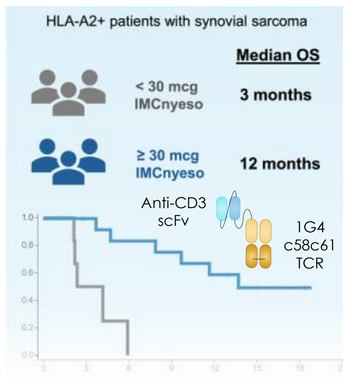
1G4 TCR recognition



Adapted from Zoete, V. et al., (2013) Front Immunol

Chain	Germline	CDR1	CDR2	CDR3
Alpha	TRAV21	DSAIYN	IQSSQRE	AVRPTSGGSYIPT
Beta	TRBV6-5	MNHEY	SVGAGI	ASSYVGNTGELF

High-affinity variant in the clinic

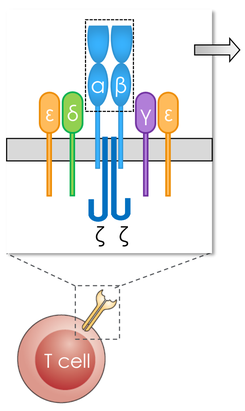


Adapted from Lopez, J.S. et al. (2025) Cell Rep Med

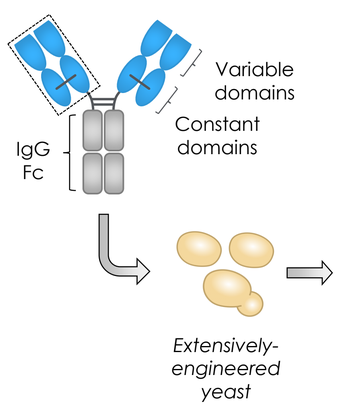
Patient-derived 1G4 TCR targets a cancer-restricted NY-ESO-1 peptide presented by HLA-A2 through specific interactions with its complementarity determining regions (CDRs) and has been affinity matured for use in a soluble TCR-based T cell engager currently in clinical trials.

Methods – Yeast-based TCR expression platform

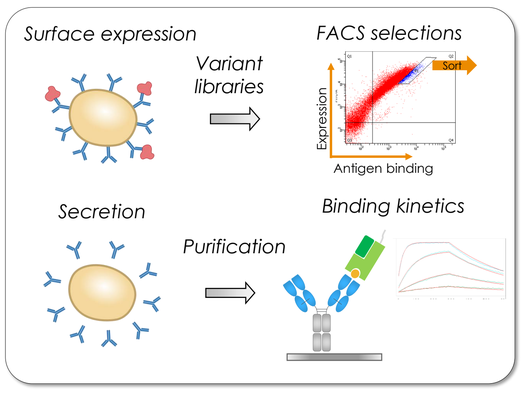
TCR-CD3 complex



TCR-Fc

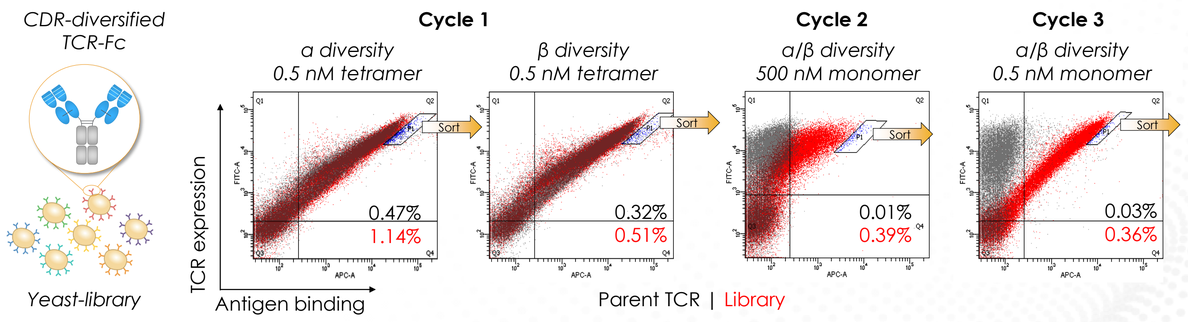


High-throughput yeast-based platform



Yeast-based platform for high-throughput discovery and characterization of soluble TCRs expressed on the yeast surface or secreted in an Fc-linked bivalent format.

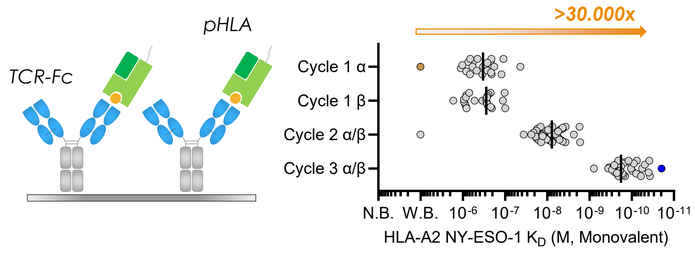
Methods – Affinity maturation of 1G4 TCR



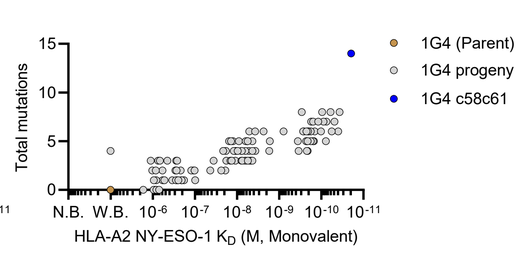
Affinity maturation of 1G4 TCR across iterative cycles of alpha- and beta-chain CDR diversification followed by FACS-based selections to enrich high-affinity TCR variants

Results – Minimally mutated high-affinity TCRs

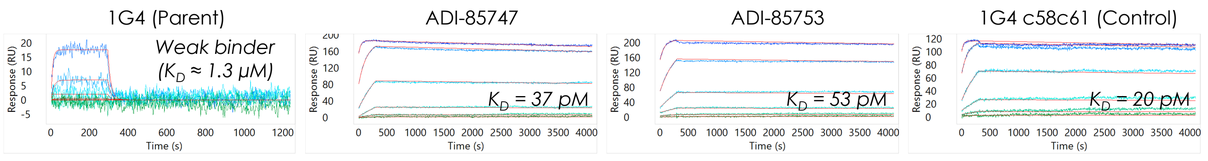
Greatly enhanced affinity over parent



Minimally-mutated TCRs



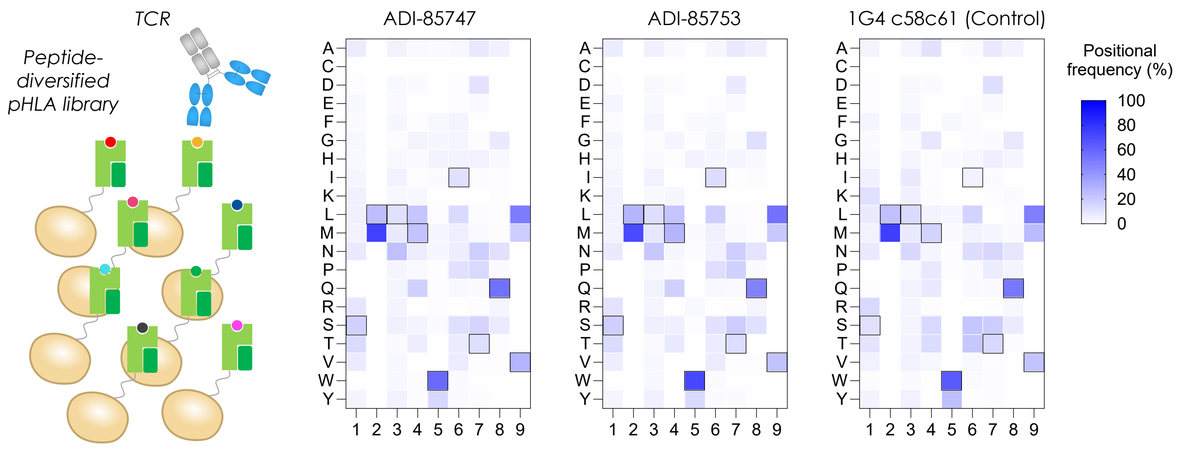
Top clones parallel high-affinity clinical control



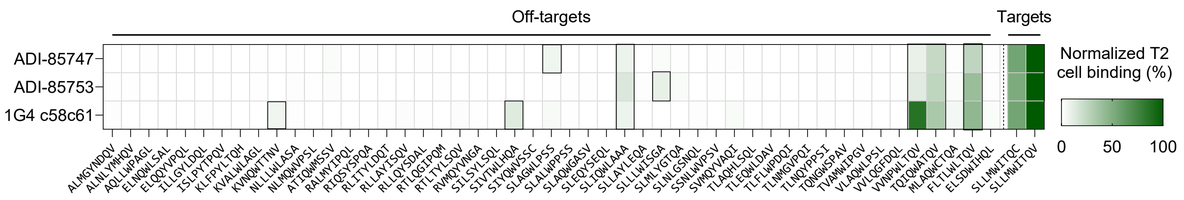
1G4 TCR affinity maturation yields progeny with greatly enhanced affinities but far fewer mutations than a related high-affinity clinical control.

Results – Enhanced specificity over clinical control

High-affinity TCRs retain selective peptide recognition

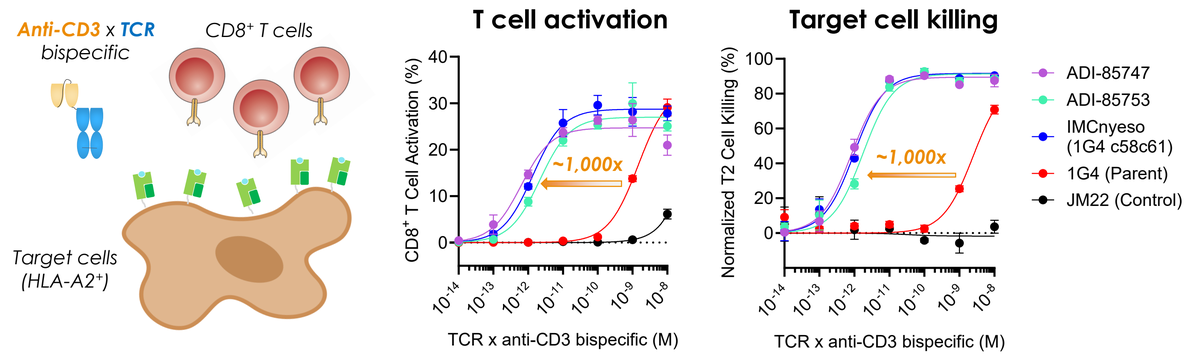


Library-derived TCRs exceed specificity of clinical control



Library-derived high-affinity 1G4 TCR variants display superior specificity in binding to a panel of human off-target peptides predicted by pHLA-library-derived recognition motifs.

Results – Potent TCE-mediated target cell killing



Library-derived high-affinity 1G4 TCR variants expressed in a clinically validated TCE format mediate highly-potent T cell activation and target cell killing equivalent to a clinical control.

Summary

- Adimab's high-throughput yeast-based platform enables rapid generation and characterization of high-affinity soluble TCR for use in pHLA-targeting therapeutics.
- Affinity maturation of a cancer-targeting TCR yielded variants with >30,000-fold improved affinities and far fewer mutations than a high-affinity clinical control.
- Library-derived high-affinity TCR variants exhibited highly specific peptide binding, with fewer human off-target interactions than a related clinical control.
- Library-derived high-affinity TCR variants potently induced target cell killing equivalent to a clinical control when reformatted into a clinically validated TCE format.

Acknowledgements

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