

Enhanced T-cell receptors for therapeutic interventions

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Natural T-cell receptor (TCR) interactions with peptide-MHC exhibit a wide range of affinities ($K_D = 0.1-500 \mu\text{M}$). Phage display and directed evolution can be used to super-enhance these affinities ($K_D \sim 10 \text{ pM}$). These enhanced TCRs, which bind to antigen with a half-life measured in days rather than seconds, can be used to count specific peptide antigens at the cell surface. We have developed mechanisms for efficient transduction of primary T-cells that result in exclusive expression of the transduced TCR chains at the T-cell surface enabling a complete redirection of T-cell specificity without the potential issue of TCR chain mispairing. We have used CD8^+ T-cells transduced with an enhanced affinity TCR to control HIV infection *in vitro*. Further developments have enabled sensitive and specific eradication of virally infected targets using soluble TCR via a highly sensitive T-cell engaging redirected lysis mechanism. We have also demonstrated that, on average, natural TCRs against ubiquitous tumour antigens bind with $\sim 100\text{X}$ lower affinity than anti-pathogen TCRs. There is clearly significant potential for utilizing enhanced TCRs in cellular and molecular therapies for infection and cancer.