403 RAPID AND MULTIPLEXED IDENTIFICATION OF NOVEL TCRS FOR TCR-T CELL THERAPY

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Background T cell receptor (TCR)-based therapeutics have displayed clinical proof-of-concept, however challenges remain to robustly identify both novel targets and therapeutically active TCRs against endogenous targets.

Methods Here, we have developed a multi-plexed platform to efficiently identify novel TCRs towards non-mutated, tumor specific targets. We have developed a functional expansion protocol, combined with single cell sequencing, that enables the discovery of diverse TCRs in both function and sequence to multiple targets simultaneously.

Results These novel TCRs are highly sensitive, with sub-nanomolar EC50s. Furthermore, these novel TCRs display in vitro killing of target-bearing cells. To interrogate the specificity of these TCRs, we utilized 3T-TRACE, a highly diverse pHLA-target library platform to identify potential cross-reactive peptides that could identify potential liabilities pre-clinically. We find that although sequence distinct TCRs display the same on-target reactivity, they vary considerably in their cross-reactivity.

Conclusions Altogether, we have developed a robust platform to identify and select therapeutically active TCRs for TCR-T based therapy.

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