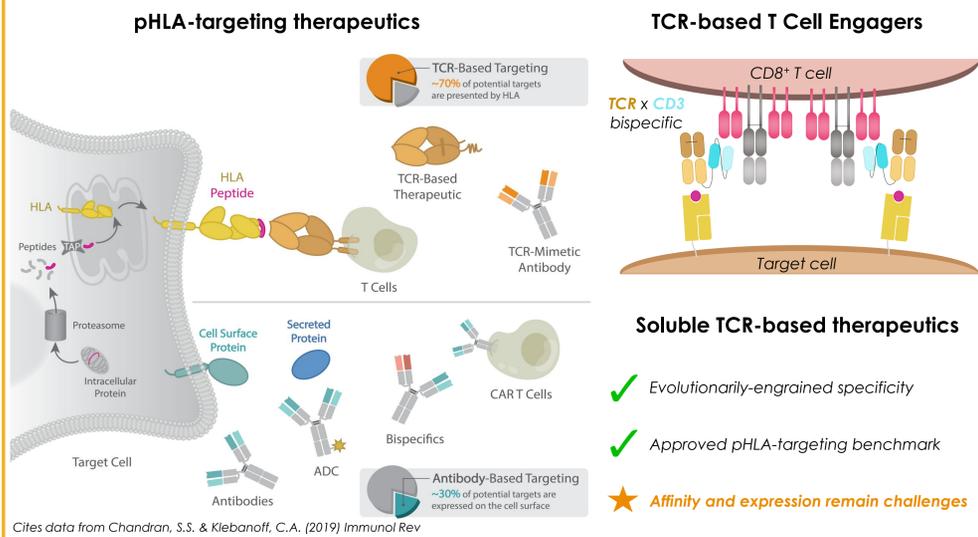


HIGH-THROUGHPUT DISCOVERY OF RARE ANTI-TUMOR TCRs VIA SYNTHETIC YEAST-BASED LIBRARIES

ADIMAB

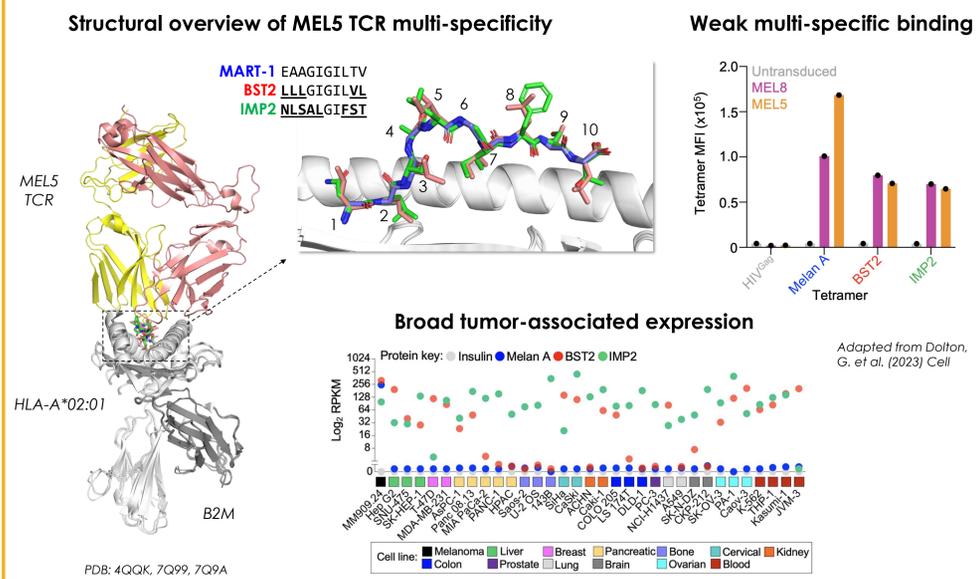
Joseph Brouillard, Tse-Han Kuo, Vivien Qiao, Akila Katuwawala, Nicholas Luey, Jonas Spaulding, Mrunal Sakharkar, Patricia Sackett, Whitney Renaud, Morgan Morrill, Allie LeMay, Hannah Green, John Horangic, Shu Lin, Beth Sharkey, Christin Strong, Elizabeth Parker, Tushar Jain, James Geoghegan, Arvind Sivasubramanian, Eric Krauland, C. Garrett Rappazzo

BACKGROUND – TCR-BASED T CELL ENGAGERS



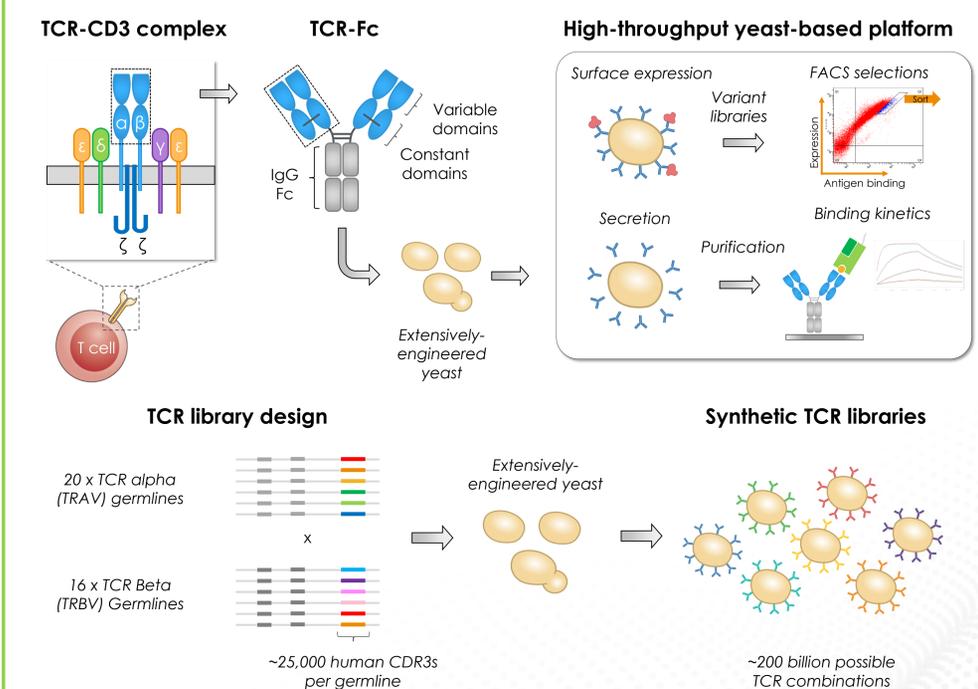
Soluble TCR-based T cell engagers enable potent and specific targeting of otherwise inaccessible intracellular antigens via peptide-HLA recognition and redirected T cell killing, yet low affinity and poor expression complicate their development.

BACKGROUND – MULTI-SPECIFIC ANTI-TUMOR TCRs



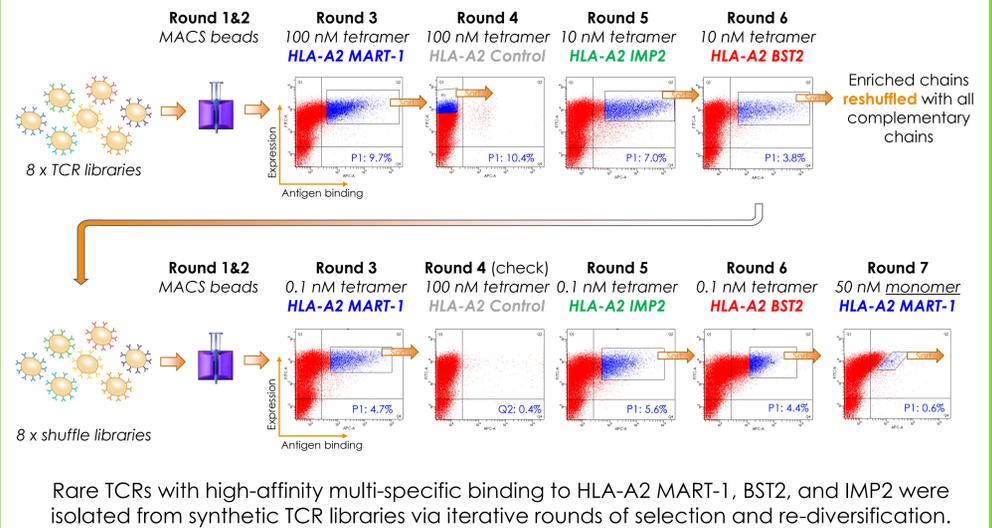
Rare patient-derived TCRs (e.g. MEL5) display weak binding to three broadly-expressed HLA-A2 restricted tumor-associated antigens MART-1 (Melan A), BST2, and IMP2, motivating discovery of high-affinity TCRs for broad and potent multi-epitope tumor targeting.

METHODS – YEAST-BASED SYNTHETIC TCR LIBRARIES

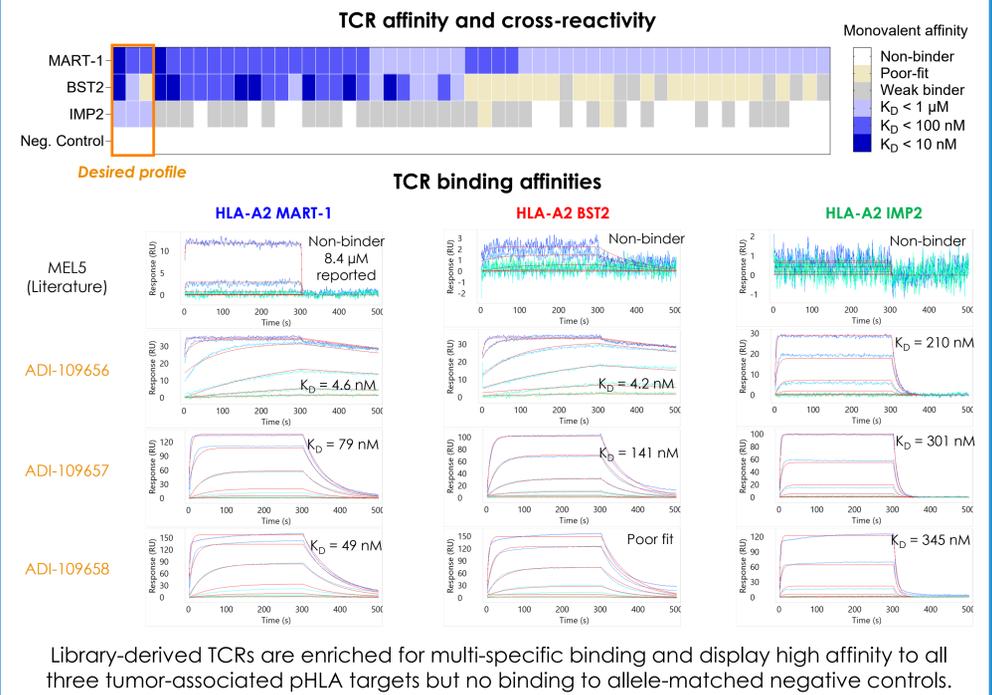


Generation of large and diverse fully-human synthetic TCR libraries built in yeast for rapid discovery and characterization of Fc-linked soluble TCRs in a high-throughput yeast platform.

METHODS – DISCOVERY OF RARE MULTI-SPECIFIC TCRs

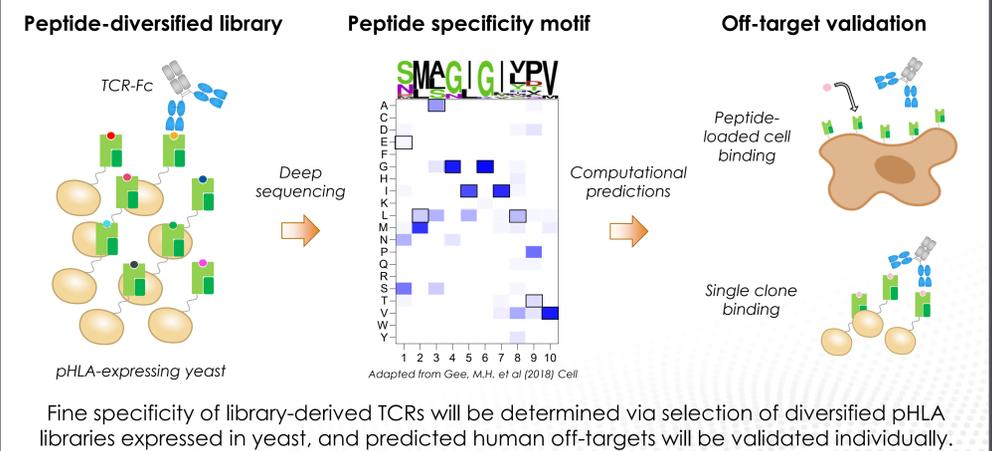


RESULTS – HIGH-AFFINITY MULTI-SPECIFIC TCRs



Library-derived TCRs are enriched for multi-specific binding and display high affinity to all three tumor-associated pHLA targets but no binding to allele-matched negative controls.

NEXT STEPS – FINE SPECIFICITY ASSESSMENTS



Fine specificity of library-derived TCRs will be determined via selection of diversified pHLA libraries expressed in yeast, and predicted human off-targets will be validated individually.

CONCLUSIONS

- Rare patient-derived TCRs exhibit specificity for three broadly-expressed HLA-A2 restricted tumor-associated antigens but possess insufficient affinity for use in soluble TCR-based T cell engager therapeutics.
- Tailored selections of fully-human TCR libraries built in yeast yield synthetic TCRs with high-affinity multi-specific binding to all three tumor-associated pHLA targets, providing new opportunities for broad and potent multi-epitope tumor targeting.
- Future work will investigate the specificity of library-derived TCRs to ensure their selectivity.
- Identification of rare high-affinity anti-tumor TCRs against other pHLA targets is ongoing.