T-cell receptor (TCR)-based immunotherapy has emerged as a promising perspective for cancer treatment. Here we present a novel and powerful TCR discovery platform allowing high throughput identification of specific TCRs directed against specific for tumor-associated peptide-HLA (pHLA) targets. Identification and development of validated tumor targets and target-restricted TCRs at Immatics is based on a combination of cutting-edge technologies to identify a broad TCR space for predefined targets and subsequently qualify those TCRs for clinical applications. These TCRs build the basis for adoptive T cell therapies, like Immatics’ ACTengine program, and are subjected to further development, including affinity maturation, for bispecific TCR-based therapeutics.

TCR Characterization Stage I: Initial Qualification

Identified TCRs undergo initial characterization including functional avidity (EC50) and analysis of binding characteristics based on position-specific mutations leading to ala-scanning, and in some instances towards normal tissue peptides from our XPRESIDENT™ database. Relevant normal-tissue peptides are selected based on their sequence in comparison to the original target peptide. A very broad TCR binding motif and clean specificity screen qualifies TCRs for further development. Narrower binding motifs and less clean specificity screens classify TCRs as potential 2nd line candidate and justify exclusion of TCR from further analyses.

TCR Characterization Stage II: Efficacy and Safety

Intensive testing of similar peptides refines TCR-specificity analysis and minimizes potential risks of off-target toxicity for TCRs with promising functional avidity and affinity. TCR validation includes the analysis of TCR-mediated responses towards target positive and negative cells. Efficacy is determined by the analysis of target-positive tumor cell lines, to show that frontline TCRs can recognize endogenously expressed target pHLA. Target pHLA copy numbers on tumor cell lines are determined by our proprietary AbsQuantTM process and reflect different target levels on primary tumor. Then, safety is analyzed to show absence of unpredicted toxicity. Therefore, absence of reactivity of TCR of interest-expressing cells towards different cell types from healthy tissues or iPSC-derived cell lines is analyzed.

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