Adoptive transfer of T-cell-receptor (TCR)-transduced T cells has shown promising results for cancer treatment, but has also produced severe immunotoxicities caused by on-target as well as off-target TCR recognition. Off-target toxicities are related to the ability of a single T cell to cross-recognize and respond to several different peptide-major histocompatibility complex (pMHC) antigens; a property that is essential for providing broad antigenic coverage despite a confined number of unique TCRs in the human body. However, this degeneracy makes it incredibly difficult to account for the range of targets that any TCR might recognize, which represents a major challenge for the clinical development of therapeutic TCRs. The prospect of using affinity-optimized TCRs has been impeded due to observations that affinity enhancement might alter the specificity of a TCR, thereby increasing the risk that it will cross-recognize endogenous tissue. Strategies for selecting safe TCRs for the clinic have included functional assessment after individual incubations with tissue-derived primary cells or with peptides substituted with single amino acids. However, these strategies have not been able to predict cross-recognition sufficiently, leading to fatal cross-reactivity in clinical trials. Novel technologies have emerged that enable extensive characterization of the exact interaction points of a TCR with pMHC, which provides a foundation from which to make predictions of the cross-recognition potential of individual TCRs. This review describes current advances in strategies for dissecting the molecular interaction points of TCRs, focusing on their potential as tools for predicting cross-recognition of TCRs in clinical development.