A Novel Method to Optimize CAR T-Cell Therapy by Targeting CD25+ T-Cell Malignancies Through Bispecific Aptamer-Mediated ScFv Engagement

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T-cell malignancies contribute significantly to the high mortality rates of lung and colon cancers, two of the deadliest globally. Current CAR T-cell therapies, while promising, suffer from over 50% off-target toxicity, leading to complications and limiting their clinical application. This study aims to develop a bispecific aptamer that binds CD25+ cancerous T-cells and CAR T-cell scFv with high affinity, ensuring precise targeting and preventing off-target cell destruction. 15 aptamers were created by gathering stable sequences from a paper by Dr. Zhang and modifying their secondary structures to fit CD25+. The aptamer and receptor structures were built by AlphaFold, a deep-learning-based tool that predicts protein structures with high accuracy. Molecular-docking simulations were accomplished using HDOCK2, a powerful receptor-ligand docking tool. Given their strength and stability, the binding energy was further calculated using Prodigy software to assess receptor-aptamer interactions. This interaction was further analyzed by the Protein-Ligand Interaction Profiler (PLIP). It offered insights into the nature of the interactions, which consisted of hydrogen bonds, hydrophobic interactions, and salt bridges. Based on the PLIP analysis, aptamer A15 for CD25 and A8 for scFv are the most appropriate candidates because they bind effectively to CD25 and scFv, eliminating chances for off-target effects. This study demonstrates that precise targeting of the receptor-aptamer interaction can effectively minimize off-target effects, making treatments safer for patients. Present findings will contribute to developing new therapeutic strategies for T-cell malignancies utilizing bispecific aptamers. Such approaches improve precision and reduce off-target damage, making CAR-T safer.

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