In Silico Modeling of Bispecific Dual-Affinity Re-Targeting (DART) Molecules Targeting PD-1 and LAG-3 for Solid Tumor Immunotherapy

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Solid tumors represent approximately 90% of adult human cancers and arise from the uncontrolled growth of cells in tissues or organs. Recently, immunotherapy that boosts the immune system's ability to fight cancer has gained significant attention. A promising therapeutic approach is the Dual-Affinity Re-Targeting (DART) molecule, which simultaneously targets two distinct immune checkpoint receptors to overcome immunosuppressive signaling and enhance immune system activation. DART can bind to two targets and simultaneously eliminate their inhibitory effects on the immune system. LAG-3 and PD-1 receptors are expressed on the surface of T cells, suppressing immune surveillance, and thereby inhibiting their ability to recognize and attack tumors. We hypothesize that scFv 1p4i binds strongly to both PD1 and LAG3 receptors, forming a bispecific DART that simultaneously binds to increase immune activation in T cells. The receptors were modeled using the UniProt and AlphaFold 3 web servers. 15 humanized single-chain variable fragments (scFv) were selected from the SAbPred web server and downloaded from the Protein Data Bank. Next, multiple configurations of the interactions between the receptors (LAG-3 and PD-1) and the scFv were computed and analyzed by the HDOCK and PLIP web servers. The receptor-scFv binding affinity was calculated to identify the most effective binding combinations (8dy1) based on interaction strength and stability. The results were subsequently validated through molecular dynamics simulations. Targeting inhibitory immune checkpoint proteins enables the efficient eradication of solid tumors and the rapid activation of an immune response against cancer cells, thereby paving the way for dual-targeted strategies that enhance therapeutic efficacy.

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