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RATIONAL DESIGN OF A TRISPECIFIC T-CELL ENGAGERS (TRITE) CONSISTING OF NANOBODIES 9G8 AND ANTI-CD3 ALONG WITH HLA-A*0201-WT1 FUSION FOR TREATMENT OF EGFR-RELATED CANCERS

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The epidermal growth factor receptor (EGFR) is aberrantly activated by various mechanisms like receptor overexpression, mutation, ligand-dependent receptor dimerization, ligand-independent activation and is associated with development of variety of tumors. Therefore, specific EGFR inhibition is one of the key targets for cancer therapy. Two major approaches have been developed and demonstrated benefits in clinical trials for targeting EGFR; monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs). However, total cure of patients with EGFR-related cancer is still a field of challenge. Although use of bispecific T-cell engagers (BiTE) have previously been introduced as interesting therapeutic platforms, patients with EGFR overexpression/mutation do not still profit from treatment with such antibodies. This might be because of the large size of BiTE antibodies, and thereby, their adverse properties. In this project, for the first time, trispecific Tcell engagers (TriTEs) consisting of nanobodies 9G8 and anti-CD3 along with HLA-A*0201 fused to Wilms' tumor 1 (WT1) peptide epitope were designed for the treatment of EGFR-related cancers utilizing various computational approaches. In agreement with this approach, few reports have also reported for design of trispecific killer engagers (TriKE) in cancer immunotherapy implying an emerging perspective of this strategy in cancer treatment. After analysis of HLA-A*0201 structure presenting WT1 peptide, the main residues involved in interactions with T-cell receptors (TCR) were identified. To generate HLA-A*0201-WT1 fusion, the WT1 peptide was inserted in a region of this HLA-type that caused no significant change in its 3D structures. Subsequently, the nanobodies and engineered HLA-type were fused using optimal Glycine linkers. By using optimal linkers, 3D structure of each nanobody and engineered HLA-A*0201 was preserved. Biological activity of this TriTE was validated *in silico* utilizing molecular docking studies and molecular dynamics simulations carried out by Haddock and Gromacs tools, respectively. This designed TriTE can be highly capable of recruiting T-cells to the EGFR-related cancer cells and subsequently activate their response against cancer cells.

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