Autologous NKG2D CAR-CD3zeta-DAP10-expressing T-Lymphocytes CYAD-01

National Cancer Institute

Source

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A preparation of autologous peripheral blood T-lymphocytes (PBTLs) that have been genetically modified and transduced with a retroviral vector to express a chimeric antigen receptor (CAR) encoding full-length human natural-killer group 2, member D receptor protein (NKG2D or KLRK1) fused to the CD3zeta cytoplasmic signaling domain and containing the naturally-expressed adaptor molecule DNAX-activating protein of 10 kDa (DAP10), with potential immunostimulating and antineoplastic activities. Upon infusion back into the patient, autologous NKG2D CAR-CD3zeta-DAP10-expressing T-lymphocytes CYAD-01 specifically recognize and bind to tumor cells expressing NKG2D ligands. This induces secretion of pro-inflammatory cytokines and results in the lysis of NKG2D ligand-expressing tumor cells. In addition, CYAD-01 targets, binds to and kills NKG2D ligand expressing tumor-associated endothelial cells in the neovasculature and immunosuppressive cells, such as regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment (TME) that express NKG2D ligands. It also activates macrophages within the TME. Ligands for NKG2D, such as MHC class I chain-related protein A (MICA), MICB, and members of the UL16-binding proteins (ULBP)/retinoic acid early transcript 1 (RAET1) family, are overexpressed on infected cells and most cancer cell types, but are not expressed on most normal, healthy cells. NKG2D, a dimeric, type II transmembrane protein expressed on human natural killer (NK) and certain T-cells, in association with the natural adaptive protein DAP10, promotes the elimination of NKG2D ligand-expressing cells. The CD3zeta signaling domain and DAP10 provide co-stimulatory signaling upon ligand binding, enhance the secretion of pro-inflammatory cytokines in response to binding to NKG2D ligand-expressing tumor cells and enhances T-cell cytotoxicity. DAP10 also associates with and stabilizes NKG2D, which facilitates expression of the NKG2D-CAR-CD3zeta construct at the cell surface.