Autologous PD-1 Antibody-expressing Mesothelin-specific CAR-T Cells

National Cancer Institute

Source

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Genetically modified, autologous T-lymphocytes that express an antibody that targets the negative immunoregulatory human cell surface receptor programmed cell death protein 1 (PD-1; PDCD1; CD279) and are transduced with a gene encoding a chimeric antigen receptor (CAR) specific for the human tumor-associated antigen (TAA) mesothelin, with potential immunomodulating and antineoplastic activities. After isolation, transduction, expansion in culture, and reintroduction into the patient, the autologous PD-1 antibody expressing mesothelin specific CAR-T cells specifically target and kill mesothelin-expressing tumor cells. The anti-PD-1 expressed on the CAR-T cells binds to PD-1 expressed on T-cells and prevents the interaction of PD-1 with its ligand programmed cell death 1 ligand 1 (PD-L1, PD-1L1; CD274) expressed on cancer cells, which prevents PD-1-mediated signaling and T-cell exhaustion, enhances T-cell activation, and results in enhanced toxicity in mesothelin-expressing tumor cells. PD-1, an immunoglobulin (Ig) superfamily transmembrane protein and inhibitory receptor, negatively regulates T-cell activation and overexpression within the tumor microenvironment and inhibits T-cell function. Mesothelin, a cell surface glycoprotein involved in cell adhesion, is overexpressed in a variety of cancer cell types.