Autologous NY-ESO-1-redirected CRISPR-edited T Cells

National Cancer Institute

Source

National Cancer Institute. Autologous NY-ESO-1-redirected CRISPR-edited T Cells. NCI Thesaurus. Code C154288.

A preparation of human autologous T-lymphocytes that are transduced with a lentiviral vector (LV) encoding a T-cell receptor (TCR) specific for the tumor-associated antigen (TAA) cancer-testis antigen NY-ESO-1 and gene-edited with the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 nuclease complex to eliminate endogenous TCR and programmed cell death 1 (PD-1) expression, with potential immunostimulating and antineoplastic activities. The CRISPR guide RNA (gRNA) specifically targets and binds to complementary sites on TCRalpha, TCRbeta and PD-1. In turn, Cas9 cleaves these specific DNA sites, thereby disrupting transcription. Upon isolation, transduction, electroporation with TCRalpha, TCRbeta and PD-1 gRNAs which are complexed to Cas9 RNA to disrupt expression of endogenous TCRalpha, TCRbeta and PD-1, expansion ex vivo, and reintroduction into the patient, the anti-NY-ESO-1 TCR LV-transduced CRISPR-edited autologous T-cells recognize and bind to NY-ESO-1-overexpressing tumor cells. This may result in a specific cytotoxic T-lymphocyte (CTL)-mediated killing of NY-ESO-1-positive tumor cells. NY-ESO-1, a tumor-associated antigen (TAA), is found in normal testis and on the surface of various tumor cell types, and is not, or is minimally, expressed in normal, healthy cells. PD-1, an immune checkpoint receptor expressed on T-cells, plays a key role in tumor immune evasion by binding to its ligand programmed cell death ligand 1 (PD-L1) expressed on tumor cells. By removing PD-1 from T-cells, PD-1-mediated signaling is halted which may decrease T-cell exhaustion and may enhance T-cell activity against the NY-ESO-1-expressing tumor cells. Removal of endogenous TCR reduces TCR competition for expression, increases the persistence and function of the expressed transgenic TCR, enhances resistance to T-cell exhaustion and increases T-cell activity.