Autologous CISH-inactivated TILs

National Cancer Institute

Source

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A preparation of autologous tumor-infiltrating lymphocytes (TILs) where the cytokine-inducible SH2-containing protein gene (CISH) has been inactivated using the clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR associated protein 9 (Cas9) editing system, containing guide RNA (gRNA) coupled to a recombinant form of the DNA endonuclease Cas9, with potential immunomodulating and antineoplastic activities. Using the CRISPR/Cas9 system, the autologous TILs are transfected, ex vivo, with a plasmid encoding for a gRNA that site-specifically targets and binds to the human CISH gene. Cas9 cleaves these specific DNA sites, which causes double strand breaks, disrupts the gene encoding CISH and prevents transcription. Upon intravenous administration, the autologous CISH-inactivated TILs are able to induce a T-cell-mediated immune response against tumor cells. CISH, a member of the suppressor of cytokine signaling family (SOCS; cytokine-induced STAT inhibitor; STAT-induced STAT inhibitor; SSI), is induced by T-cell receptor (TCR) stimulation. CISH plays a key role in the negative regulation of both T-cell signaling and CTL-mediated tumor cell eradication. The knockout of the CISH gene enhances the expansion and anti-tumor activities of effector T-cells.