Autologous CCR4-CD30CAR-CD28-CD3zeta-expressing T-Lymphocytes

National Cancer Institute

Source

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A preparation of autologous T-lymphocytes (ATL) that have been transduced with the retroviral vector SFG, a Moloney murine leukemia (Mo-MuLV) virus-based vector, encoding human C-C chemokine receptor 4 (CCR4), linked via an internal ribosome entry site (IRES), to a chimeric antigen receptor (CAR) composed of a single chain single-chain variable fragment (scFv) directed against the CD30 antigen (CAR.CD30) and linked, via the spacer human IgG1 immunoglobulin heavy constant region (hinge-CH2CH3 region), to the co-stimulatory domains of CD28 and the zeta chain of the TCR/CD3 complex (CD3-zeta) (CD28zeta), with potential immunostimulating and antineoplastic activities. Upon administration of the autologous CCR4-CD30CAR-CD28-CD3zeta-expressing T-lymphocytes, the expressed CCR4 on the T-cells allows for enhanced migration of the cells to chemokine-secreting tumor cells. The expressed CAR.CD30 moiety specifically recognizes and binds to CD30-expressing tumor cells, resulting in specific T-cell-mediated tumor cell lysis. CD30, a cell surface receptor and a member of the tumor necrosis factor (TNF) receptor superfamily, is transiently expressed on activated lymphocytes and is constitutively expressed in hematologic malignancies. CCR4, a G-coupled-protein receptor for C-C chemokines normally expressed on regulatory T-cells (Tregs) but not on cytotoxic T-lymphocytes (CTLs), is involved in chemokine-mediated cellular migration. The co-expression of CCR4 on these CTLs may enhance their anti-tumor activity compared to T-lymphocytes expressing the same CAR-CD30 receptor but without CCR4 expression.