Ad-RTS-hIL-12

National Cancer Institute

Source

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An inducible adenoviral vector encoding human pro-inflammatory cytokine interleukin-12 (IL-12; IL12), which is under the transcriptional control of the RheoSwitch Therapeutic System (RTS) (Ad-RTS-hIL-12), with potential immunomodulating and antineoplastic activities. RTS consists of two fusion proteins: Gal4-EcR, which contains a modified ecdysone receptor (EcR) fused with the DNA binding domain of the yeast Gal4 transcription factor, and VP16-RXR, which contains a chimeric retinoid X receptor (RXR) fused with the transcription activation domain of the viral protein VP16 of herpes simplex virus type 1 (HSV1). Upon intratumoral administration of Ad-RTS-hIL-12, given in combination with the proprietary, diacylhydrazine-based activator ligand veledimex (INXN-1001), veledimex binds specifically to the EcR part of the RTS and stabilizes heterodimerization between the two fusion proteins, forming an active transcription factor, which induces the transcription of IL-12 under the control of an inducible promoter containing Gal4-binding sites. The expressed IL-12 activates the immune system by promoting the activation of natural killer cells (NK cells), inducing secretion of interferon-gamma (IFN-g) and inducing cytotoxic T-lymphocyte (CTL)-mediated responses against tumor cells, which may result in immune-mediated tumor cell lysis and inhibition of tumor cell proliferation. In the presence of veledimex, the protein heterodimer changes to a stable conformation and can bind to the inducible promoter, while without veledimex the two fusion proteins form unstable heterodimers; this allows the controlled, regulated intratumoral expression of the IL-12 gene.