

Lipid Nanoparticle Encapsulating mRNAs Encoding Human OX40L/IL-23/IL-36gamma mRNA-2752

National Cancer Institute

Source

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A lipid nanoparticle encapsulating mRNAs encoding for the human co-stimulatory protein tumor necrosis factor ligand superfamily member 4 (TNFSF4; OX40 Ligand; OX40L), the pro-inflammatory cytokines interleukin-23 (IL-23) and interleukin-36gamma (IL-36gamma), with potential immunomodulatory and anti-tumor activities. Upon intratumoral (IT) injection of the lipid nanoparticle encapsulated mRNAs encoding human OX40L/IL-23/IL-36gamma mRNA-2752, the lipid nanoparticle binds to the plasma membrane of cells and releases the mRNAs into the cell. The OX40L mRNA is then translated by the cellular protein translation machinery to produce OX40L protein, which is then expressed on the plasma membrane of the cells that internalized the OX40L mRNA. OX40L binds to and activates signaling pathways downstream of its cognate receptor tumor necrosis factor receptor superfamily member 4 (TNFRSF4; OX40), which is expressed on activated T-cells. OX40L/OX40 binding promotes increased cytokine production, which can induce proliferation of memory and effector T-lymphocytes against the nearby tumor cells. The co-administration of IL-23 and IL-36gamma further stimulates anti-tumor immune responses. Altogether, this may enhance T-cell mediated anti-tumor immune responses thereby killing of the tumor cells. OX40L, a cell surface glycoprotein and member of the tumor necrosis factor (TNF) ligand superfamily, provides a co-stimulatory signal for the proliferation and survival of activated T-cells. IL-36gamma activates innate immune cells and promotes T-helper 1 (Th1) responses, whereas IL-23 has been implicated in Th1/Th17 immunity as well as in the modulation of antigen-presenting cells (APCs).