

Therapeutic agents to treat cancer and neurodegenerative disease via a cell signaling target

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Technology description

Cytokines play a central role in a wide range of biological systems by allowing intercellular communication. They interact with the target cells by binding to the specific receptors on the plasma membrane and this triggers the associated intracellular kinases to phosphorylate signaling proteins. The purpose of this invention is to provide a new compositions and methods using cytokine polypeptides useful for treating neurodegenerative diseases and cancer.

Disease indication- Cancer and neurodegenerative diseases.

Drug format- Engineered proteins which could be administered either directly or through nucleic acids/cells that express the polypeptides. The soluble polypeptides could also be used in companion diagnostic applications to characterize tumors and identify patients whose disorder is associated with this pathway.

Drug class- First-in-class. There are no known small molecule, antibody or biologic modulators of Ciliary Neurotrophic Factor Receptor (CNTFR) and/or Cardiotrophin-like Cytokine Factor 1 (CLCF1) in clinical or pre-clinical development as a cancer therapy. There are no known biologic agents based on CLCF1 in clinical or pre-clinical development for treating neurological diseases.

Research Stage and Preliminary Data- The inventors have engineered variant polypeptides that bind CNTFR with increased affinity relative to the wild-type proteins. Using a mouse model of non-small cell lung cancer, they demonstrated that treating mice with these peptides decreased tumor burden compared to controls.

Target- There are two separate inventions that impact the CNTFR signaling pathway – receptor-based binders and ligand-based binders. Stanford Docket S16-371 includes variants of the CLCF1 ligand that bind CNTFR and modulate receptor activity. Stanford Docket S16-371 includes variants of CNTFR that are designed to bind to CLCF1 and modulate ligand activity.

Background and Mode of Action- CLCF1 is a soluble cytokine in the IL-6 family that is involved in cell proliferation and survival. CLCF1 binds to CNTFR on cells to form a complex with LIFR and gp130. This complex then activates downstream signaling pathways that lead to activation of STAT3, cell proliferation, survival and differentiation. The CLCF1 is secreted by cancer-associated fibroblasts in the tumor microenvironment and is received as a growth signal by tumor cells expressing CNTFR. For example, functional studies have identified a role for CLCF1-CNTFR signaling in promoting growth of non-small cell lung cancer (NSCLC). Other studies have shown that CNTFR and its cognate ligands

support neuron survival. For example, CNTF has been shown to have a direct neuroprotective effect on degenerating motor neurons in stress-induced conditions. Engineered CLCF1 protein ligands can bind CNTFR to function as either an agonist or antagonist for STAT3 phosphorylation resulting in activation or inhibition of CNTFR activity. Alternatively, soluble CNTFR receptors are engineered to modulate CNTFR activity by binding the ligand.

Keywords- therapeutic: cell signaling, cancer therapeutics, neurotrophic factor, neurodegenerative diseases, suppressor of cytokine signaling

Application area

Cancer therapeutics

Neurodegenerative disease therapeuticsCancer diagnostics

Assays to characterize CLCF1 and CNTFR in tumor cells and their microenvironment

Advantages

First in class- this is a new mechanism of action for cancer treatment

Optimized binding- engineered proteins are designed to increase or decrease affinity to the targets and other molecules to reduce off-target effects and potentially improve the safety profile or efficacy

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