Inhibition of CNTFR signaling in treatment of cancer

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Technology description

Tumor microenvironment, or stroma, has been increasingly discovered to have a critical role in tumor initiation and progression. Cells in stroma communicate with tumor cells to assist tumor angiogenesis, immune tolerance, drug resistance, metastasis, and tumor growth. One of the mechanisms of such interaction is secretion of soluble molecules such as cytokines or growth factors. The purpose of this invention is to provide a new method of detection and modulation of a cancer associated cytokine as a cancer therapy.
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.
Target- There are two separate inventions that impact the CNTFR signaling pathway – receptor binders and ligand binders. Stanford Docket S16-371 includes variants of the CLCF1 ligand as well as other molecules that could bind CNTFR and modulate receptor activity. Stanford Docket S16-371 includes variants of CNTFR as well as other molecules that are designed to bind to the ligand and modulate CLCF1 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 with CNTFR to act as either an agonist or antagonist for STAT3 phosphorylation to activate or

deactivate 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 therapeuticsNeurodegenerative 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 treatmentOptimized 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

Institution

Stanford University

Inventors

Eric Alejandro Sweet-Cordero
Jennifer Cochran
Jun Kim

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com