Docket #: S18-098

Potent LIF Receptor "Trap" as Cancer Therapeutic

Stanford researchers in the Cochran Lab have patented a potential pancreatic cancer therapeutic approach using novel agents that bind tightly to and inhibit a cancer factor called LIF (leukemia inhibitory factor). The endogenous receptors of LIF are used as starting scaffolds for engineering heightened affinity towards LIF. Circulation half-life and affinity are improved by fusion to the Fc domain of an antibody. The mutations engineered into each receptor are novel and have never been used in combination before, nor have they been incorporated into a LIF receptor or gp130 Fc-fusion construct. Initial results indicate these engineered LIF receptor polypeptides are the tightest LIF binders in existence, which should lead to strong efficacy. This LIF receptor "trap" has better targeting, tighter binding, longer circulation time, and therefore potentially stronger efficacy than other antibody treatments – addressing an unmet medical need for a variety of cancers, particularly pancreatic cancer, a deadly malignancy with few approved therapeutic options.

Stage of Development

Treatment with the engineered LIFR Fc-fusion polypeptides (eLIFR-Fc) potently inhibits LIF signaling and slows pancreatic tumor growth in vitro and in vivo. Specifically, western blot results of lysates from PANC1 (human pancreatic cancer cell line) indicate that the Cochran Lab engineered LIFR polypeptides can reduce LIF-mediated pSTAT3 levels in cancer cells, even when incubated in only ~3 fold excess, and to completely ablate LIF signaling when incubated at greater excess, as would be relevant therapeutically. The degree of inhibition is improved over the Anti-LIF mAb, L1. Potent signal inhibition was also observed in KP4 human pancreatic cancer cells. Treatment with eLIFR-Fc significantly decreased in vitro sphere formation of KP4 pancreatic cancer cells compared with control treatments and slowed KP4 tumor growth in vivo in a xenograft flank model. Together, these data position eLIFR-Fc as a potent and specific inhibitor of LIF signaling capable of abrogating tumor growth in a disease indication with few therapeutic options.

Applications

- Cancer therapeutic, either alone or in combination with existing standard of care
- Diagnostic tool for detection of LIF in the serum of pancreatic cancer patients, potentially enabling early detection of disease

Advantages

- Provides specific blockade of receptor binding sites by using receptors themselves as inhibitors
- Able to bind to two faces of LIF at once for improved inhibition
- Very high affinity for the target (over 20-fold greater than the wild-type receptor)
- Significant binding advantage over antibody approaches
- Fusion to the Fc domain of an antibody allows for extended blood half-life but rapid target clearance (24-48 hours).
- Likely no off-target toxicity as a therapeutic

Publications

- Hunter, S. A., McIntosh, B. J., Shi, Y., Sperberg, R. A. P., Funatogawa, C., Labanieh, L., ... & Cochran, J. R. (2021). An engineered ligand trap inhibits leukemia inhibitory factor as pancreatic cancer treatment strategy. *Communications Biology, 4*(1), 452. https://doi.org/10.1038/s42003-021-01928-2

Patents

- Published Application: WO2020018932
- Published Application: 20210300992
- Issued: 12,049,490 (USA)

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