Docket #: S23-081

High-affinity Decoy Cytokines for IL-11 Receptor Super-agonism and Antagonism

Stanford researchers have developed a high-affinity IL-11 decoy cytokine for super-agonism and antagonism of the IL-11 receptor, enabling the treatment of a wide variety of diseases from inflammatory disease to cancer as well as research into IL-11 signaling pathways.

Interleukin-11 (IL-11) signaling plays a significant role in many diseases through its roles in inflammation, tissue repair, and cancer progression. For example, IL-11 blocking antibodies are in clinical development for pulmonary fibrosis while wild-type IL-11 is approved as a treatment for thrombocytopenia. However, stronger binders to the IL-11 receptor have the potential to be more effective treatments.

Stanford researchers therefore developed an IL-11 decoy cytokine with much higher affinity for the IL-11 receptor than the wild-type cytokine. High-throughput combinatorial screening identified mutations to IL-11 that increased its binding affinity to the IL-11 receptor 70-fold. Researchers identified additional mutations that converted this super-agonist to an antagonist by ablating binding to the gp130 co-receptor. Finally, they identified other mutations that enabled high-affinity binding to the mouse IL-11 receptor (~10-fold over wildtype) without affecting human IL-11 receptor binding. This engineered cytokine slows the growth of tumors in a mouse model of non-small cell lung cancer.

Stage of Development
In vivo: In mouse models of non-small cell lung cancer, treatment with the engineered cytokine slowed tumor growth in a dose-dependent manner

Applications

- IL-11 antagonists, for the treatment of *e.g.* cancer, inflammatory disease, and fibrotic disease
- IL-11 agonists, for the treatment of *e.g.* thrombocytopenia
- Research in IL-11 signaling

Advantages

- Highly specific for the IL-11 receptor
- High affinity binding to the human IL-11 receptor (~70-fold higher than endogenous IL-11)
- High affinity binding to the mouse IL-11 receptor (~10-fold higher than endogenous mouse IL-11) to enable research in mouse models
- Small size allows for diffusion into tumors (~19 kDa cytokine vs ~150 kDa antibodies)

Publications

- Brianna J. McIntosh, Griffin G. Hartmann, et al. (2023). An engineered interleukin?11 decoy cytokine inhibits receptor signaling and proliferation in lung adenocarcinoma. Bioengineering and Translatoinal Medicine, 8(6):e10573.

Patents

- Published Application: WO2024259282

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