

~~BISPECIFIC~~ IL-2- AND ANTI-PD-1-BASED THERAPEUTICS AND METHODS OF USE THEREOF

FIELD

[0001] The present disclosure relates generally to IL2-based therapeutics and methods of use thereof and more specifically to a fusion protein comprising an IL2 moiety and an antigen-binding moiety that binds specifically to human PD-1 as well as methods of use thereof.

BACKGROUND

[0002] Interleukin 2 (IL-2 or IL2) is a pluripotent cytokine produced primarily by activated T cells. It stimulates the proliferation and differentiation of T cells, induces the generation of cytotoxic T lymphocytes (CTLs) and the differentiation of peripheral blood lymphocytes to cytotoxic cells and lymphokine-activated killer (LAK) cells, promotes cytokine and cytolytic molecule expression by T cells, facilitates the proliferation and differentiation of B-cells and the synthesis of immunoglobulin by B-cells, and stimulates the generation, proliferation, and activation of natural killer (NK) cells (see Waldmann, 2006, *Nat Rev Immunol* 6:595-601 and Malek, 2008, *Annu Rev Immunol* 26:453-79). IL2 is involved in the maintenance of peripheral CD4⁺ CD25⁺ regulatory T (Treg) cells (see, e.g., Fontenot *et al.*, 2005, *Nature Immunol* 6:1142-51), which are also known as suppressor T cells. They suppress effector T cells from destroying their (self-)target, either through cell-cell contact by inhibiting T cell help and activation or through release of immunosuppressive cytokines such as IL-10 or TGF β . Depletion of Treg cells was shown to enhance IL2-induced anti-tumor immunity (Imai *et al.*, 2007, *Cancer Sci* 98:416-23).

[0003] However, IL2 is not optimal for inhibiting tumor growth due to its pleiotropic effects. The use of IL2 as an antineoplastic agent has been limited by the serious toxicities that accompany the doses necessary for a tumor response. Proleukin® (marketed by Prometheus Laboratories, San Diego, Calif.) is a recombinant form of IL2 that is approved for the treatment of metastatic melanoma and metastatic renal cancer, but its side effects are so severe that its use is only recommended in a hospital setting with access to intensive care. The major side effect of IL2 therapy is vascular leak syndrome (VLS), which leads to the accumulation of interstitial fluid in the lungs and liver, resulting in pulmonary edema and liver damage. There is no treatment for VLS other than withdrawal of IL2. It has been shown that IL2-induced pulmonary edema resulted from direct binding of IL2 to lung endothelial cells, which express low to intermediate levels of functional high-affinity IL2 receptors (Krieg *et al.*, 2010, *Proc Nat Acad*