METHODS OF USING INTERLEUKIN-2 AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Nos. 63/121,726, filed December 4, 2020, and 63/283,822, filed November 29, 2021. The contents of the aforementioned applications are hereby incorporated by reference in their entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on December 1, 2021, is named P2029-7042WO_SL.txt and is 1,728,569 bytes in size.

BACKGROUND

Interleukin-2 (IL-2) is a cytokine that regulates the activities of the immune system. It is produced by leukocytes, such as T cells, natural killer (NK) cells, dendritic cells, and macrophages, in response to antigenic or mitogenic stimulation. IL-2 is important for T cell proliferation, B cell stimulation, and other activities associated with immunity and tolerance. It is part of the body's adaptive immune response and discriminates between foreign and host antigens. IL-2 mediates its effects by binding to IL-2 receptors, which in turn activate downstream signaling events.

Human IL-2 is an-FDA approved drug for the treatment of diseases such as metastatic renal carcinoma and melanoma. The use of IL-2 in eligible patients is sometimes restricted due to the severe toxicity associated with IL-2 therapy, and only a small subset of eligible patients will actually receive therapy. The toxicities associated with IL-2 therapy can include severe fever, nausea, vomiting, vascular leak and serious hypotension. Despite these toxicities, however, IL-2 is typically effective for its approved indications.

For patients with various diseases and conditions that are amenable to treatment with IL-2, there continues to be an unmet need for novel IL-2-based agents that exhibit characteristics sufficient for the development of a safe and efficacious therapeutic.

SUMMARY

In one aspect, provided herein is use of an IL-2 agent in the manufacture of a medicament for treating or preventing a skin transplantation rejection in a subject, wherein the IL-2 agent is an IL-2 fusion protein comprising an IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5.

In another aspect, provided herein is use of an IL-2 agent in the manufacture of a medicament for conditioning a subject prior to a skin transplantation, wherein the IL-2 agent is an IL-2 fusion

protein comprising an IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5.

In another aspect, provided herein is use of an IL-2 agent in the manufacture of a medicament for inducing and/or modulating (*e.g.*, increasing) immunosuppression in a subject, wherein the subject has undergone, is undergoing, or will receive a skin transplantation, wherein the IL-2 agent is an IL-2 fusion protein comprising an IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5.

In another aspect, provided herein is use of an IL-2 agent in the manufacture of a medicament for selectively increasing T regulatory cells in a subject, wherein the subject has undergone, is undergoing, or will receive a skin transplantation, and wherein the IL-2 agent is an IL-2 fusion protein comprising an IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5.

In another aspect, provided herein is an IL-2 agent for use as a medicament in combination with a skin transplantation, wherein the IL-2 agent is an IL-2 fusion protein comprising an IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5.

In yet another aspect, provided herein is use of an IL-2 agent in the manufacture of a medicament for: (i) preventing a skin transplantation rejection in a subject; (ii) inducing and/or modulating (e.g., increasing) immunosuppression in a subject; or (iii) selectively increasing T regulatory cells in a subject, wherein the IL-2 agent is an IL-2 fusion protein comprising an IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5, and wherein the medicament is to be used in combination with a skin transplantation.

This disclosure provides, at least in part, IL-2 agents (*e.g.*, IL-2 variants, IL-2 fusion proteins, IL-2 complexes, and IL-2 conjugates) that comprise one or more amino acid alterations (*e.g.*, substitutions) in IL-2, and that comprise one or more of the structural or functional properties disclosed herein. In an embodiment, nucleic acid molecules encoding the IL-2 agents, expression vectors, host cells, compositions (*e.g.*, pharmaceutical compositions), kits, containers, and methods for making the IL-2 agents, are also provided. The IL-2 agents disclosed herein can be used (alone or