

In an aspect, the disclosure features the use of an IL-2 agent in the manufacture of a medicament for selectively increasing p-STAT5 signaling, wherein the medicament increases the level of p-STAT5 signaling in a Treg cell from a subject and wherein the medicament does not substantially increase the level of p-STAT5 signaling in a NK cell and/or a cytotoxic T cell from the subject, 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, the disclosure the use of an IL-2 agent in the manufacture of a medicament for increasing p-STAT5 signaling, wherein the medicament is to be contacted with a Treg cell from a subject having a disorder in an amount sufficient to increase the level of p-STAT5 signaling in the Treg cell, compared to a reference level of p-STAT5 signaling, wherein the reference level is the level of p-STAT5 signaling in a Treg cell from a subject who does not have the disorder, and wherein the Treg cell from the subject who does not have the disorder has been contacted with the same amount of the IL-2 agent, 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, the disclosure features the use of an IL-2 agent in the manufacture of a medicament for treating a disorder in a subject, wherein the medicament increases the level of phospho-STAT5 (p-STAT5) signaling in a Treg cell from the 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, the disclosure features the use of an IL-2 agent in the manufacture of a medicament for treating immune-related focal segmented glomerulosclerosis (IM-FSGS), 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 an aspect, the disclosure features a method of treating a disorder, comprising administering to a subject in need thereof an effective amount of an IL-2 agent described herein, such that the level of phosphor-STAT5 (p-STAT5) signaling in a Treg cell from the subject is increased, thereby treating the disorder.

In an embodiment, the level of p-STAT5 signaling in the Treg cell is increased by at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold.

In an embodiment, the level of p-STAT5 signaling in a NK cell and/or a cytotoxic T cell from the subject is not substantially increased. In an embodiment, the level of p-STAT signaling in the NK cell and/or cytotoxic T cell is increased by no more than 50%, 40%, 30%, 20%, or 10%.

In an embodiment, the disorder is, or the subject has, a disorder described herein. In an embodiment, the disorder is, or the subject has, lupus nephritis. In an embodiment, the disorder is, or the subject has, psoriasis. In an embodiment, the disorder is, or the subject has, an autoimmune

disorder, e.g., an autoimmune disorder described herein. In an embodiment, the disorder is, or the subject has, systemic lupus erythematosus (SLE), autoimmune hepatitis (AIH), immune-related focal segmented glomerulosclerosis (IM-FSGS), or alopecia areata (AA).

In an embodiment, the method further comprises determining the level of p-STAT5 signaling in an immune cell (e.g., in a T reg cell, an NK cell, and/or a cytotoxic T cell) from the subject. In an embodiment, the method further comprises isolating a blood cell (e.g., a PBMC) from the subject.

In an embodiment, the determining step is performed prior to, during, and/or subsequent to the contacting or administering step. In an embodiment, the level of p-STAT5 signaling is determined using a flow cytometry-based p-STAT5 assay, e.g., as described in Example 13.

In an embodiment, the IL-2 agent comprises an IL-2 variant comprising: (i) the amino acid substitution H16L or H16N, and/or the amino acid substitution I92S, and (ii) the amino acid substitutions V69A, Q74P, and C125S, corresponding to human IL-2 (SEQ ID NO: 1031). In an embodiment, the IL-2 variant further comprises the amino acid substitution T3A. In an embodiment, the IL-2 variant comprises the amino acid sequence of any of SEQ ID NOs: 4, 5, 11, 1000, 1001, or 1002, an amino acid sequence that is at least 95% identical thereto or differs by no more than 1, 2, 3, 4, or 5 amino acids therefrom, or a functional fragment thereof.

In an embodiment, the IL-2 agent comprises an IL-2 fusion protein comprising the IL-2 variant. In an embodiment, the IL-2 fusion protein further comprises an Fc region. In an embodiment, the Fc region comprises an Fc region of IgG1 allotype m3 comprising an N297G substitution according to EU numbering. In an embodiment, the Fc region comprises the amino acid sequence of SEQ ID NO: 1003, or an amino acid sequence that is at least 95% identical thereto or differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids therefrom, or a functional fragment thereof. In an embodiment, the Fc region is fused to the C-terminus of the IL-2 variant. In an embodiment, the IL-2 fusion protein further comprises a linker. In an embodiment, the linker