Thus, in one aspect, the present invention refers to the use of a human interleukin-2 (IL-2) mutein or a Fc-fusion protein comprising an Fc and the human interleukin-2 (IL-2) mutein, wherein the human interleukin-2 (IL-2) mutein comprises a V91K substitution and an amino acid sequence set forth in SEQ ID NO:1, in the manufacture of a medicament for increasing the ratio of regulatory T cells (Tregs) to non-regulatory T cells within a population of T cells to treat an autoimmune or inflammatory disorder. In another aspect, the present invention refers to a method of monitoring the response of a subject to treatment with the human interleukin-2 (IL-2) mutein as defined in the appending claim set, or the Fc-fusion protein as defined in the appending claim set, comprising detecting a change in said subject, said change being: a) an increase in body temperature, b) an increase in CRP in said subject's peripheral blood measured in a sample obtained from said subject, c.) a decrease in platelets in said subject's peripheral blood in a sample obtained from said subject, d) a decrease in neutrophils in said subject's peripheral blood in a sample obtained from said subject, or e) a decrease in albumin in said subject's peripheral blood in a sample obtained from said subject, wherein said treatment is to be terminated, suspended, reduced in dosing frequency, or reduced in dosing amount after said change is detected. The IL-2 muteins described herein have a minimal numbers of alterations to IL-2, thereby decreasing the likelihood of creating an immune response against the IL-2 mutein and/or endogenous IL-2, yet maintain Treg preferential expansion and activation. Moreover, in certain examples, the IL-2 mutein is fused to a molecule, e.g. an antibody Fc, that increases the serum half-life when administered to a subject. IL-2 muteins have a short serum half-life (3 to 5 hrs for sub-cutaneous injection). Exemplary IL-2 mutein Fc fusions described herein have a half-life in humans of at least 1 day, at least 3 days, at least 5 days, at least 10 days, at least 15 days, at least 20 days, or at least 25 days. This effect on the pharmacokinetics of the IL-2 muteins allows for decreased or less frequent dosing of the IL-2 mutein therapeutic.

Claims

What is claimed is:

1. Use of a human interleukin-2 (IL-2) mutein or a Fc-fusion protein comprising an Fc and the human interleukin-2 (IL-2) mutein, wherein the human interleukin-2 (IL-2) mutein comprises a V91K substitution and an amino acid sequence set forth in SEQ ID NO: 1, in the manufacture of a medicament for increasing the ratio of regulatory T cells (Tregs) to non-regulatory T cells within a population of T cells to treat an autoimmune or inflammatory disorder.

2. The use of claim 1, wherein position 125 is an alanine.

3. The use of claim 1, wherein position 125 is a cysteine.

4. The use of any one of claims 1-3, wherein the Fc is a human IgG1 Fc.

5. The use of claim 4, wherein the human IgG1 Fc comprises a substitution at N297.

6. The use of claim 5, wherein the substitution at N297 is N297G.

7. The use of any one of claims 1-6, comprising a substitution or deletion of the C-terminal lysine of said human IgG Fc.

8. The use of claim 7, wherein the C-terminal lysine of said human IgG Fc is deleted.

9. The use of any one of claims 1-8, wherein a linker connects the Fc and human IL-2 mutein portions of said protein.

10. The use of claim 9, wherein the linker is GGGGS (SEQ ID NO: 5), GGNGT (SEQ ID NO: 6), and YGNGT (SEQ ID NO: 7).

11. The use of claim 10, wherein the linker is GGGGS (SEQ ID NO: 5).

12. The use of any one of claims 1-11, wherein said Fc-fusion protein comprises an Fc dimer.

13. The use of claim 12, wherein said Fc-fusion protein comprises two IL-2 muteins.

14. The use of claim 12, wherein said Fc-fusion protein comprises a single IL-2 mutein.

15. The use of any one of claims 1-14, wherein the autoimmune or inflammatory disorder is selected from the group consisting of inflammation, atopic diseases, paraneoplastic autoimmune diseases, cartilage inflammation, arthritis, rheumatoid arthritis, juvenile arthritis, juvenile rheumatoid arthritis, pauciarticular juvenile rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, juvenile ankylosing spondylitis, juvenile enteropathic arthritis, juvenile reactive arthritis, juvenile Reiter's Syndrome, SEA Syndrome (Seronegativity, Enthesopathy, Arthropathy Syndrome), juvenile dermatomyositis, juvenile psoriatic arthritis, juvenile scleroderma, juvenile systemic lupus erythematosus, juvenile vasculitis, pauciarticular rheumatoid arthritis, polyarticular rheumatoid arthritis, systemic onset rheumatoid arthritis, ankylosing spondylitis, enteropathic arthritis, reactive arthritis, Reiter's Syndrome, dermatomyositis, psoriatic arthritis, scleroderma, vasculitis, myolitis, polymyolitis, dermatomyolitis, polyarteritis nodossa, Wegener's granulomatosis, arteritis, ploymyalgia rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, Sjogren's syndrome, psoriasis, plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, dermatitis, atopic dermatitis, atherosclerosis, lupus, Still's disease, Systemic Lupus Erythematosus (SLE), myasthenia gravis, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, celiac disease, multiple sclerosis (MS), asthma, COPD, , rhinosinusitis, rhinosinusitis with polyps, eosinophilic esophogitis, eosinophilic bronchitis, Guillain-Barre disease, Type I diabetes mellitus, thyroiditis, Addison's disease, Raynaud's phenomenon, autoimmune hepatitis, graft-versus-host disease (GVHD), transplantation rejection, kidney damage, hepatitis C-induced vasculitis, and spontaneous loss of pregnancy.

16. The use of claim 15, wherein the disorder is selected from the group consisting of lupus, graft-versus-host disease (GVHD), hepatitis C-induced vasculititis, Systemic Lupus Erythematosus (SLE), rheumatoid arthritis, psoriasis, Crohn's disease, ulcerative colitis, celiac disease, multiple sclerosis (MS), Type I diabetes mellitus, spontaneous loss of pregnancy, atopic diseases, and inflammatory bowel diseases.

17. A method of monitoring the response of a subject to treatment with the human interleukin-2 (IL-2) mutein as defined in any one of claims 1-14, or the Fc-fusion protein as defined in any one of claims 1-14, comprising detecting a change in said subject, said change being:

a) an increase in body temperature,

b) an increase in CRP in said subject's peripheral blood measured in a sample obtained from said subject,

c.) a decrease in platelets in said subject's peripheral blood in a sample obtained from said subject,

d) a decrease in neutrophils in said subject's peripheral blood in a sample obtained from said subject, or

e) a decrease in albumin in said subject's peripheral blood in a sample obtained from said subject,

wherein said treatment is to be terminated, suspended, reduced in dosing frequency, or reduced in dosing amount after said change is detected.

18. The method of claim 17, wherein said change comprises:

a) an increase in body temperature of at least 0.5° C,

b) an increase in CRP in said subject's peripheral blood of at least 0.2 mg/mL,

c) a decrease in platelets in said subject's peripheral blood of at least 0.8-fold,

d) a decrease in neutrophils in said subject's peripheral blood of at least 0.8-fold, or

e) a decrease in albumin in said subject's peripheral blood of at least 0.4-fold.