

What is Claimed is:

1. Use of a synthequine polypeptide that binds to the extracellular domains of two or more cytokine receptor polypeptides in a non-natural combination in the manufacture of a medicament to modulate immune responsiveness in an individual by selective activation of a non-natural combination of cytokine receptor polypeptides present on an immune cell,

wherein the synthequine polypeptide comprises two or more binding domains each of which binding domain comprises a monovalent antibody that binds to the extracellular domain of a subunit of different multimeric cytokine receptors, wherein the cytokine receptors comprise an intracellular domain comprising at least one JAK/STAT binding sequence;

wherein the first and second cytokine receptor subunits do not naturally multimerize in response to contacting the cell with a naturally occurring cytokine ligand;

and contact of the immune cell with the synthequine polypeptide causes multimerization of the cytokine receptor subunits and activation of JAK/STAT-mediated signaling in the cell from the non-natural combination of receptor polypeptides;

and wherein the medicament comprises a therapeutically effective amount of the synthequine to modulate immune responsiveness in the individual.

2. The use of claim 1, where the cytokine receptors are selected from βc , γc , IL-3R α , β IL-3R, GM-CSFR α , IL-5R α , CNTF α , CRLF1, LIFR α , gp130, IL-6R α , IL-11R α , OSMR β , IL-2R α , IL-2R β , IL-2R γ , IL-4R α , IL-7R α , IL-9R α , IL-13R α , IL-15R α , IL-21R α , IFNAR2, IL-23R, EpoR, IL-12R β , IFNAR1, G-CSFR, c-MPLR.

3. The use of claim 2, wherein a synthequine binds to two of such receptors, and activates JAK/STAT signaling.

4. The use of claim 2, wherein a synthequine binds to three of such receptors and activates JAK/STAT signaling.

5. The use of any of claims 1-4, wherein the synthequine comprises binding domains with binding affinity for the ECD of the receptor subunit of less than $1 \times 10^{-7}M$.

6. The use of claim 5, wherein the binding domains are directly joined.

7. The use of claim 5, wherein the binding domains are joined through a linker.
8. The use of any of claims 1-7, wherein the monovalent antibodies are VHs.
9. The use of any of claims 1-8 wherein the binding domains are joined by a peptide linker comprising from 2-100 amino acids.
10. The use of any of claims 1-9, wherein the binding domains are joined by a non-peptide linker.
11. A synthequine comprising at least two binding domains, wherein a first binding domain specifically binds to the extracellular domain of a first cytokine receptor polypeptide and wherein a second binding domain specifically binds to the extracellular domain of a second cytokine receptor polypeptide, wherein said first and second cytokine receptor polypeptides are not naturally associated and wherein the first and second binding domains comprise monovalent antibodies;
wherein the cytokine receptors comprise an intracellular domain comprising at least one JAK/STAT binding sequence;
wherein the first and second cytokine receptor subunits do not naturally multimerize in response to contacting the cell with a naturally occurring cytokine ligand;
and wherein upon contact of an immune cell with the synthequine polypeptide the cytokine receptor subunits multimerize and activate JAK/STAT-mediated signaling in the cell from the non-natural combination of receptor polypeptides.
12. The synthequine of claim 11 wherein the cytokine receptor is selected from the group consisting of: βc , γc , IL-3R α , β IL-3R, GM-CSFR α , IL-5R α , CNTF α , CRLF1, LIFR α , gp130, IL-6R α , IL-11R α , OSMR β , IL-2R α , IL-2R β , IL-2R γ , IL-4R α , IL-7R α , IL-9R α , IL-13R α , IL-15R α , IL-21R α , IFNAR2, IL-23R, EpoR, IL-12R β , IFNAR1, G-CSFR, and c-MPLR.
13. The synthequine of claim 11 or claim 12, wherein the at least first and second binding domains are directly joined.
14. The synthequine of any of claims 11-13, wherein the at least first and second binding domains are joined via a linker.

15. The synthequine of any of claims 11 - 14 wherein at least one monovalent antibody is a VHH.

16. A nucleic acid sequence encoding the synthequine of any of claims 11-15.

17. A recombinant vector comprising the nucleic acid sequence of claim 16.

18. A recombinant host cell comprising the nucleic acid sequence of claim 16.