

What is Claimed is:

1. A method for selective activation of a non-native combination of receptor polypeptides in a cell, the composition comprising a syntheKine that binds to the extracellular domain of two or more receptor polypeptides in a non-native combination thereby causing multimerization of the receptors polypeptides and activation of signaling.

2. The method of claim 1, wherein the syntheKine comprises a polypeptide.

3. The method of claim 1 or claim 2, wherein the receptor polypeptide(s) are one or more of (i) a cytokine receptor that activates the JAK/STAT pathway in the cell; (ii) a receptor tyrosine kinase; or (iii) a TNFR superfamily member.

4. The method of claim 3, 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.

5. The method of claim 4, wherein a syntheKine binds to two of such receptors, and activates JAK/STAT signaling.

6. The method of claim 4, wherein a syntheKine binds to three of such receptors and activates JAK/STAT signaling.

7. The method of claim 3, where the receptor tyrosine kinase proteins are selected from EGFR, ErbB2, ErbB3, ErbB4, InsR, IGF1R, InsRR, PDGFR α , PDGFR β , CSF1R/Fms, cKit, Flt-3/Flk2, VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3, FGFR4, PTK7/CCK4, TrkA, TrkB, TrkC, Ror1, Ror2, MuSK, Met, Ron, Axl, Mer, Tyro3, Tie1, Tie2, EphA1-8, EphA10, EphB1-4, EphB6, Ret, Ryk, DDR1, DDR2, Ros, LMR1, LMR2, LMR3, ALK, LTK, SuRTK106/STYK1.

8. The method of claim 7, wherein a syntheKine binds to two of such receptors, and activates signaling.

9. The method of claim 3, where the TNFR superfamily member is selected from TNFR1 (TNFRSF1A), TNFR2 (TNFRSF1B; TNFRSF2), 41-BB (TNFRSF9); AITR (TNFRSF18); BCMA (TNFRSF17), CD27 (TNFRSF7), CD30 (TNFRSF8), CD40 (TNFRSF5), Death Receptor 1 (TNFRSF10C), Death Receptor-3 (TNFRSF25), Death Receptor 4 (TNFRSF10A), Death Receptor 5 (TNFRSF10B), Death Receptor -6 (TNFRSF21), Decoy Receptor-3 (TNFRSF6B), Decoy Receptor 2 (TNFRSF10D), EDAR, Fas (TNFRSF6), HVEM (TNFRSF14), LT α -R (TNFRSF3), OX40 (TNFRSF4), RANK (TNFRSF11A), TACI (TNFRSF13B), Troy (TNFRSF19), XEDAR (TNFRSF27), Osteoprotegerin (TNFRSF11B), TWEAK receptor (TNFRSF12A), BAFF Receptor (TNFRSF13C), NGF receptor (TNFRSF16).

10. The method of claim 9, wherein the synthekine binds to two or more of such receptors and activates signaling.

11. The method of any of claims 1-10, wherein the synthekine comprises binding domains with high affinity for two distinct extracellular domains of a receptor set forth in claim 3.

12. The method of claim 11, wherein the binding affinity is less than about 1×10^{-7} M.

13. The method of claim 11, wherein the binding domains are directly joined.

14. The method of claim 11, wherein the binding domains are joined through a linker.

15. The method of any of claims 1-14, wherein the binding domain is a mutated form of a native ligand.

16. The method of any of claims 1-14, wherein the binding domain is a de novo designed binding domain.

17. The method of any of claims 1-14, wherein the binding domain is an antibody derived binding protein.

18. The method of any of claims 1-14, wherein the binding domain is a nanobody derived binding domain.

19. The method of any of claims 1-14, wherein the binding domain is a knottin-engineered scaffold.

20. The method of any of claims 1-19 wherein the binding domains are joined by a peptide linker comprising from 2-100 amino acids.

21. The method of any of claims 1-19, wherein the binding domains are joined by a non-peptide linker.

22. A syntheKine for use in the methods of any of claims 1-21.

23. A pharmaceutical composition comprising a syntheKine of claim 22, and a pharmaceutically acceptable excipient.