CLAIMS

1. A recombinant pro-protein comprising:
   a. a recombinant polypeptide comprising a cleavable moiety that is a substrate for a protease, wherein the cleavable moiety comprises the amino acid sequence selected from the group consisting of SEQ ID NO: 198 or a functional variant of SEQ ID NO: 198 in which one or two amino acids are substituted in SEQ ID NO: 198; and
   b. a polypeptide with biological activity.

2. The recombinant pro-protein of claim 1, wherein the polypeptide with biological activity comprises a cytokine, chemokine, growth factor, a soluble receptor, antigen-binding polypeptide, an antibody or an antigen-binding portion thereof, or a combination thereof.

3. The recombinant pro-protein of claim 1, wherein the cleavable moiety that is a substrate for a protease SEQ ID NO: 198 in which one or two amino acids are substituted in SEQ ID NO: 198 with the provison that the amino acid at positions 4 and 5 of SEQ ID NO: 198 are not substituted.

4. The recombiant pro-protein of claim 1, wherein the cleavable moiety that is a substrate for a protease links the polypeptide with biological activity to another amino acid sequence.

5. The recombinant pro-protein of claim 1, wherein the pro-protein has attenuated biological activity, and wherein cleavage of the cleavable moiety by the protease produces a polypeptide with biological activity that is not attenuated.

6. The recombinant pro-protein of claim 1, further comprising a blocking moiety selected from a steric blocking moiety, a specific blocking moiety, and a combination thereof.

7. The recombinant pro-protein of claim 6, wherein the blocking moiety comprises a steric blocking moiety that comprises human serum albumin (HSA), an anti-HSA antibody, an immunoglobulin Fc, or a fragment of any of the foregoing .

8. The recombinant pro-protein of claim 6, wherein the blocking moiety comprises a specific blocking moiety that comprises an antibody that has binding specificity for the biologically active polypeptide or an antigen-binding fragment thereof, or the ligand-binding portion of a receptor that has binding specificity for the biologically active polypeptide or a ligand-binding fragment thereof.

9. The recombinant pro-protein of claim 1, further comprising a half-life extension domain.

10. The recombinant pro-protein of claim 5, wherein the polypeptide with biological activity comprises at least one of an extracellular domain, a transmembrane domain, and an intracellular domain.

11. The recombinant pro-protein of claim 1, wherein the polypeptide with biological activity comprises at least one of an extracellular domain, a transmembrane domain, and an intracellular domain.

12. The recombinant pro-protein of claim 1, wherein the polypeptide with biological activity comprises a cell surface receptor, a chimeric antigen receptor (CAR), or a T Cell Receptor (TCR) subunit.

13. The recombinant pro-protein of claim 1, wherein the polypeptide with biological activity comprises an antigen-binding polypeptide, an antibody or an antigen-binding portion thereof.

14. The recombinant pro-protein of claim 1, wherein one or two amino acid substitutions in the functional variant of SEQ ID NO: 198 are conservative substitutions.

15. The recombinant pro-protein of claim 1, wherein the functional variant of SEQ ID NO: 198 comprises the amino acid sequence of SEQ ID NO: 199, SEQ ID NO: 370, SEQ ID NO: 381, SEQ ID NO: 382, SEQ ID NO: 383, or SEQ ID NO: 390.

16. The recombinant pro-protein of claim 1, wherein the functional varaint of SEQ ID NO: 198 is a substrate for Cathepsin L.

17. A nucleic acid composition comprising one or more nucleic acids encoding a recombinant pro-protein comprising:

a. a recombinant polypeptide comprising, a cleavable moiety that is a substrate for a protease, wherein the cleavable moiety comprises the amino acid sequence of SEQ ID NO: 198 or a functional variant of SEQ ID NO: 198 in which one or two amino acids are substituted in SEQ ID NO: 198; and

b. a polypeptide with biological activity.

18. The nucleic acid composition of claim 17, wherein the polypeptide with biological activity comprises a cytokine, chemokine, growth factor, a soluble receptor, antigen-binding polypeptide, an antibody or an antigen-binding portion thereof, or a combination thereof.

19. The nucleic acid composition of claim 17, wherein the cleavable moiety that is a substrate for a protease comprises an amino acid sequence at least 85% identical to SEQ ID NO: 198 in which one or two amino acids are substituted in SEQ ID NO: 198 with the provison that the amino acid at positions 4 and 5 of SEQ ID NO: 198 are not substituted.

20. The nucleic acid composition of claim 17, wherein the cleavable moiety that is a substrate for a protease links the polypeptide with biological activity to another amino acid sequence.

21. The nucleic acid composition of claim 17, wherein the pro-protein has attenuated biological activity, and wherein cleavage of the cleavable moiety by the protease produces a polypeptide with biological activity that is not attenuated.

22. The nucleic acid composition of claim 17, wherein the one or more nucleic acids further encode a blocking moiety selected from a steric blocking moiety, a specific blocking moiety, and a combination thereof.

23. The nucleic acid composition of claim 22, wherein the blocking moiety comprises a steric blocking moiety that comprises human serum albumin (HSA), an anti-HSA antibody, an immunoglobulin Fc, or a fragment thereof.

24. The nucleic acid composition of claim 22, wherein the blocking moiety comprises a specific blocking moiety that comprises an antibody that has binding specificity for the biologically active polypeptide or an antigen-binding fragment thereof, or the ligand-binding portion of a receptor that has binding specificity for the biologically active polypeptide or a ligand-binding fragment thereof.

25. The nucleic acid composition of claim 17, wherein the one or more nucleic acids further encodes a half-life extension domain.

26. The nucleic acid composition of claim 17, wherein the polypeptide with biological activity comprises at least one of an extracellular domain, a transmembrane domain, and an intracellular domain.

27. The nucleic acid composition of claim 17, wherein the polypeptide with biological activity comprises a cell surface receptor, a chimeric antigen receptor (CAR), or a T Cell Receptor (TCR) subunit.

28. The nucleic acid of claim 17, wherein one or two amino acid substitutions in the functional variant of SEQ ID NO: 198 are conservative substitutions.

29. The nucleic acid of claim 17, wherein the functional variant of SEQ ID NO: 198 comprises the amino acid sequence of SEQ ID NO: 199, SEQ ID NO: 370, SEQ ID NO: 381, SEQ ID NO: 382, SEQ ID NO: 383, or SEQ ID NO: 390.

30. The nucleic acid claim 17, wherein the functional varaint of SEQ ID NO: 198 is a substrate for Cathepsin L.

31. A vector comprising the nucleic acid composition of claim 17.

32. The vector of claim 31, wherein the vector is a viral vector.

33. A host cell comprising the nucleic acid of claim 17.

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