Claims

1. Use of a fusion protein in the manufacture of a medicament for treating cancer, wherein the fusion protein comprises:
(a) a first polypeptide or protein capable of translocating into an endoplasmic reticulum (ER), or a fragment thereof; and
(b) an interleukin 18 (IL-18), a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant,
wherein the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant is C-terminal to the first polypeptide or protein capable of translocating into the ER, or the fragment thereof.

2. The use according to claim 1, wherein the medicament is for treating a subject having or suspected of having cancer, or having one or more symptoms of cancer.

3. The use according to claim 1, wherein the fusion protein further comprises a targeting polypeptide.

4. The use according to claim 3, wherein the targeting polypeptide comprises a tumor-associated antigen binding domain.

5. The use according to claim 1, wherein the fusion protein further comprises an antibody or antibody fragment and is capable of binding to a tumor cell, an immune cell or stromal cell in a tumor tissue, a tumor-draining lymph node, or another secondary lymphoid organ.

6. The use according to claim 1, wherein the fusion protein further comprises a masking domain.

7. The use according to claim 6, wherein mature IL-18 or a mature IL-18 variant is releasable from the masking domain by a protease.

8. The use according to claim 7, wherein the protease is a granzyme or a metalloprotease.

9. The use according to claim 8, wherein the granzyme is released from an NK cell, a T cell, a neutrophil, or a mast cell.

10. The use according to claim 8, wherein the metalloprotease is expressed in a tumor microenvironment or tumor-draining lymph node.

11. The use according to claim 1, wherein the fusion protein further comprises a half-life-extending molecule.

12. The use according to claim 11, wherein the half-life-extending molecule comprises human serum albumin (HSA) or an HSA-binding fragment.

13. The use according to claim 1, wherein the fusion protein has reduced activity compared with wild-type IL-18 when the fusion protein is not bound to a cell comprising an IL-18 receptor complex (RC).

14. The use according to claim 13, wherein the reduced activity is at least a 75% reduction in activity compared with wild-type IL-18.

15. The use according to claim 1, wherein the medicament is for use in combination with an immunotherapeutic agent.

16. The use according to claim 15, wherein the immunotherapeutic agent comprises an immune checkpoint inhibitor.

17. The use according to claim 1, wherein the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant is fused to an N-terminus or a C-terminus of a knob-containing polypeptide of a knob-into-hole heterodimeric IgG1 protein.

18. The use according to claim 17, wherein the fusion protein further comprises a propeptide (PP) or a PP variant.

19. The use according to claim 18, wherein the PP variant comprises a polypeptide having the sequence AAEPVEDNX1INFVAMKFIDNTLYFIAEDDEN (SEQ ID NO: 238), wherein X1 is any amino acid other than cysteine.

20. The use according to claim 19, wherein X1 is valine or serine.

21. The use according to claim 18, wherein the PP or PP variant serves as a masking domain.

22. The use according to claim 1, wherein the fusion protein further comprises one or more cleavage sites cleavable by one or more proteases.

23. The use according to claim 22, wherein the one or more proteases are selected from the group consisting of EK, TEV, ADAM17, cathepsin, MMP2, MMP9, MMP14, Granzyme A, Granzyme B, Granzyme M, Granzyme K, and combinations thereof.

24. The use according to claim 1, wherein the fusion protein comprises an IL-18 variant having diminished binding to IL-18 binding protein (IL-18BP) compared with wild-type IL-18.

25. The use according to claim 24, wherein the fusion protein comprising the IL-18 variant has a binding affinity for human IL-18 receptor (IL-18R) within 30-fold of the binding affinity of wild-type IL-18 for human IL-18R.

26. The use according to claim 25, wherein a ratio of the binding affinity of the fusion protein comprising the IL-18 variant for IL-18BP to the binding affinity of the fusion protein comprising the IL-18 variant for IL-18R is no greater than 3:1.

27. The use according to claim 1, wherein the fusion protein further comprises a binding domain for a protein expressed on immune cells that express an IL-18 receptor complex or that, upon activation, express the IL-18 receptor complex.

28. The use according to claim 1, wherein the fusion protein comprises one or more sequences set forth in any one of Tables 1A, 1B, and 4.

29. Use of a fusion protein in the manufacture of a medicament for treating fibrosis, wherein the treatment comprises reducing collagen deposition into extracellular space or reducing fibrosis, and wherein the fusion protein comprises:
(a) a first polypeptide or protein capable of translocating into an endoplasmic reticulum (ER), or a fragment thereof; and
(b) an interleukin 18 (IL-18), a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant.

30. The use according to claim 29, wherein the medicament is for treating a subject having or suspected of having a fibrotic tissue environment.

31. A fusion protein comprising:
(a) a first polypeptide or protein capable of translocating into an endoplasmic reticulum (ER), or a fragment thereof; and
(b) an interleukin 18 (IL-18), a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant,
wherein the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant is C-terminal to the first polypeptide or protein capable of translocating into the ER, or the fragment thereof.

32. The fusion protein of claim 31, further comprising a targeting polypeptide.

33. The fusion protein of claim 32, wherein the targeting polypeptide comprises a tumor-associated antigen binding domain.

34. The fusion protein of claim 31, further comprising a masking domain.

35. The fusion protein of claim 34, wherein mature IL-18 or a mature IL-18 variant is releasable from the masking domain by a protease.

36. The fusion protein of claim 31, wherein the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant is fused to an N-terminus or a C-terminus of a knob-containing polypeptide of a knob-into-hole heterodimeric IgG1 protein.

37. The fusion protein of claim 36, further comprising a propeptide (PP) or a PP variant.

38. The fusion protein of claim 37, wherein the PP variant comprises a polypeptide having the sequence AAEPVEDNX1INFVAMKFIDNTLYFIAEDDEN (SEQ ID NO: 238), wherein X1 is any amino acid other than cysteine.

39. The fusion protein of claim 38, wherein X1 is valine or serine.

40. The fusion protein of claim 37, wherein the PP or PP variant serves as a masking domain.

41. The fusion protein of claim 31, further comprising one or more cleavage sites cleavable by one or more proteases.

42. The fusion protein of claim 41, wherein the one or more proteases are selected from the group consisting of EK, TEV, ADAM17, cathepsin, MMP2, MMP9, MMP14, Granzyme A, Granzyme B, Granzyme M, Granzyme K, and combinations thereof.

43. The fusion protein of claim 31, wherein the fusion protein comprises an IL-18 variant having diminished binding to IL-18 binding protein (IL-18BP) compared with wild-type IL-18.

44. The fusion protein of claim 43, wherein the fusion protein comprising the IL-18 variant has a binding affinity for human IL-18 receptor (IL-18R) within 30-fold of the binding affinity of wild-type IL-18 for human IL-18R.

45. The fusion protein of claim 44, wherein a ratio of the binding affinity of the fusion protein comprising the IL-18 variant for IL-18BP to the binding affinity of the fusion protein comprising the IL-18 variant for IL-18R is no greater than 3:1.

46. The fusion protein of claim 31, wherein one or more cysteines in the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant are modified or replaced with a natural or non-natural amino acid.

47. The fusion protein of claim 31, wherein the fusion protein comprises one or more sequences set forth in any one of Tables 1A, 1B, and 4.

48. A fusion protein comprising a mature IL-18 variant selected from Table 1B and a short polypeptide.

49. The fusion protein of claim 48, wherein the IL-18 variant is from FUSE-557, FUSE-626, FUSE-669, FUSE-670, FUSE-675, FUSE-676, FUSE-682, FUSE-683, FUSE-684, FUSE-685, FUSE-832, FUSE-882, FUSE-895, FUSE-952, FUSE-1015, FUSE-1016, FUSE-1017, FUSE-

1041, FUSE-1042, FUSE-1044, FUSE-1109, FUSE-1110, FUSE-1111, FUSE-1112, FUSE-1113, FUSE-1116, FUSE-1176, or FUSE-1177.

50. An IL-18 variant selected from Table 1B corresponding to FUSE-557, FUSE-626, FUSE-669, FUSE-670, FUSE-675, FUSE-676, FUSE-682, FUSE-683, FUSE-684, FUSE-685, FUSE-832, FUSE-882, FUSE-895, FUSE-952, FUSE-1015, FUSE-1016, FUSE-1017, FUSE-1041, FUSE-1042, FUSE-1044, FUSE-1109, FUSE-1110, FUSE-1111, FUSE-1112, FUSE-1113, FUSE-1116, FUSE-1176, or FUSE-1177.