## CLAIMS

WHAT IS CLAIMED IS:

1. A modified interleukin-18 (IL-18) polypeptide that preferentially binds IL-18 receptor (IL-18R) over IL-18 binding protein (IL-18BP) comprising:

(i) at least five mutations in at least five of the following positions: Y1, L5, K8, M51, K53, S55, Q56, P57, G59, M60, E77, Q103, S105, D110, N111, M113, V153, and N155 relative to wild type (WT) IL-18 as set forth in SEQ ID NO: 30; and

(ii) a C38S mutation and a mutation at position C68 that is C68S, C68G, C68A, C68D, or C68N, wherein said modified IL-18 preferentially binds IL-18R over IL-18BP, wherein the modified IL-18 polypeptide comprises cysteine residues at positions C76 and C127 relative to SEQ ID NO: 30, and wherein the modified IL-18 polypeptide comprises an amino acid sequence having 95% or more sequence identity with any one of SEQ ID NOs: 6, 16, 17, 19, and 21.

2. The modified IL-18 polypeptide of claim 1, wherein the mutation at position C68 is C68G, C68A, C68D, or C68N and the modified IL-18 polypeptide comprises an amino acid sequence having 95% or more sequence identity with any one of SEQ ID NOs: 16, 17, 19, and 21.

3. The modified IL-18 polypeptide of claim 1 or claim 2, wherein the mutation at position C68 is C68D and the modified IL-18 polypeptide comprises an amino acid sequence having 95% or more sequence identity with SEQ ID NO:19.

4. The modified IL-18 polypeptide of any one of claims 1-3, wherein the modified IL-18 polypeptide comprises the amino acid sequence set forth in any one of SEQ ID NOs: 6, 16, 17, 19, and 21.

5. The modified IL-18 polypeptide of any one of claims 1-4, wherein the modified IL-18 polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 19.

6. A pharmaceutical composition comprising the modified IL-18 polypeptide of any one of claims 1-5, and a pharmaceutically acceptable excipient.

7. The composition of claim 6, wherein the pharmaceutical composition is formulated for subcutaneous injection.

8. The composition of claim 6 or claim 7, comprising:

a buffering agent to maintain pH between 6.2 and 6.8,

a sugar,

a chelating agent,

an agent to prevent oxidation, and

an agent to prevent protein absorption.

9. An isolated nucleic acid comprising a nucleotide sequence encoding the modified IL-18 polypeptide of any one of claims 1-5.

10. The isolated nucleic acid of claim 9, wherein the nucleic acid is a plasmid or a viral vector.

11. The isolated nucleic acid of claim 9 or claim 10, wherein the nucleotide sequence encoding the IL-18 polypeptide is fused immediately 3' of, and in frame with, a nucleotide sequence encoding a small ubiquitin-like modifier (SUMO) tag that is cleavable by a SUMO protease.

12. The isolated nucleic acid of claim 11, wherein the SUMO protease is ULP1.

13. The isolated nucleic acid of claim 11 or claim 12, wherein the SUMO tag comprises the amino acid sequence set forth in SEQ ID NO: 26 or 27.

14. An isolated cell comprising the nucleic acid of any one of claims 9-13.

15. The isolated cell of claim 14, comprising a nucleic acid comprising a nucleotide sequence encoding a SUMO protease.

16. The isolated cell of claim 14 or claim 15, wherein the cell is a bacterial cell, a yeast cell, an engineered T or NK cell, a chimeric antigen receptor T cell (CAR-T cell), an engineered TCR-T cell, a chimeric antigen receptor NK cell (CAR-NK cell), or a Tumor-infiltrating Lymphocyte (TIL), that expresses the encoded interleukin-18 (IL-18) polypeptide.

17. The modified IL-18 polypeptide of any one of claims 1-5 or the composition of any one of claims 6-8 for use in therapy.

18. Use of the modified IL-18 polypeptide of any one of claims 1-5 or the composition of any one of claims 6-8 in the manufacture of a medicament for the treatment of a cancer or an infectious disease in an individual in need thereof.

19. A method of making an active polypeptide, comprising:

contacting, inside of a bacterial cell, an exogenously provided fusion protein with an exogenously provided SUMO (small ubiquitin-like modifier) protease, wherein the fusion protein comprises a polypeptide of interest fused at the N-terminus to a SUMO tag,

wherein, within the bacterial cell, the SUMO protease cleaves the fusion protein, thus removing the SUMO tag from the polypeptide of interest, wherein the polypeptide of interest is an IL-18 polypeptide of any one of claims 1-5 that is activated by the removal of the SUMO tag.