CLAIMS

1. A membrane-cleavable chimeric protein, oriented from N-terminal to C-terminal, having the formula:

E - L - TM or TM - L- E

wherein:

a) E comprises an effector molecule;

b) L is a first linker comprising a protease cleavage site and an amino acid sequence selected from the group consisting of: GGGGSISSGLLSGRSDNHGGGGS (SEQ ID NO: 3); GGGGSVPLSLYSGGGISSGLLSGRSDNHGGGGS (SEQ ID NO: 4); GGGGSHPVGLLARGGGHPVGLLARGGSGRSAGGSGRSAGGGGS (SEQ ID NO: 5); GGGGSHPVGLLARGGGGS (SEQ ID NO: 6); and GGGGSLAQAVRSSGGGGS (SEQ ID NO: 7), wherein L is a cleavable linker;

c) TM comprises a cell transmembrane protein; and

d) E - L - TM or TM - L- E is configured to be expressed as a single polypeptide.

2. The membrane-cleavable chimeric protein of claim 1, wherein said membrane-cleavable chimeric protein further comprises a signal peptide at the N-terminus.

3. The membrane-cleavable chimeric protein of any one of claims 1-2, wherein the effector molecule comprises a cytokine or a functional fragment thereof.

4. The membrane-cleavable chimeric protein of claim 3, wherein the cytokine is selected from the group consisting of: IL-l-beta, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-15, IL-17A, IL-18, IL-21, IL-22, Type I interferons, Interferon-gamma, and TNF-alpha.

5. The membrane-cleavable chimeric protein of claim 4, wherein the cytokine is IL-12.

6. The membrane-cleavable chimeric protein of any one of claims 1-5, wherein the effector molecule comprises p40 and p35 subunits of IL-12 linked by a second linker.

7. The membrane-cleavable chimeric protein of any one of claims 1-6, wherein the transmembrane domain is derived from the group consisting of: PDGFR-beta, CD8, CD28, CD3 zeta-chain, CD4, 4-1BB, 0X40, ICOS, CTLA-4, PD-1, LAG-3, 2B4, LNGFR, NKG2D, EpoR, TNFR2, B7-1, and BTLA.

8. The membrane-cleavable chimeric protein of any one of claims 1-7, wherein the transmembrane domain is derived from B7-1.

9. The membrane-cleavable chimeric protein of any one of claims 1-8, wherein the transmembrane domain is linked to a cytoplasmic domain.

10. The membrane-cleavable chimeric protein of claim 9, wherein the cytoplasmic domain is derived from the group consisting of: PDGFR-beta, CD8, CD28, CD3 zeta-chain, CD4, 4-1BB, 0X40, ICOS, CTLA-4, PD-1, LAG-3, 2B4, LNGFR, NKG2D, EpoR, TNFR2, B7-1, and BTLA.

11. The membrane-cleavable chimeric protein of any one of claims 9-10, wherein the cytoplasmic domain is derived from B7-1.

12. The membrane-cleavable chimeric protein of any one of claims 1-11, wherein the effector molecule is cleaved from the chimeric protein upon cleavage of the cleavable linker L.

13. The membrane-cleavable chimeric protein of any one of claims 1-12, wherein the cleavable linker L is preferentially cleaved in cancer cells.

14. The membrane-cleavable chimeric protein of any one of claims 1-13, wherein

a) when expressed in a cell, the effector molecule is tethered to a cell membrane of the cell; and/or

b) when expressed in a cell expressing a protease capable of cleaving the protease cleavage site, the effector molecule is released from the cell membrane.; and/or

c) wherein the protease expressed on the cell membrane is endogenous to the cell.

15. A nucleic acid molecule coding for the membrane-cleavable chimeric protein of any one of claims 1-14.

16. A nucleic acid molecule comprising an expression cassette wherein the expression cassette comprises a promoter and an exogenous polynucleotide sequence encoding the membrane-cleavable chimeric protein of any one of claims 1-14.

17. The nucleic acid molecule of claim 16, wherein the promoter is selected from the group consisting of a constitutive promoter, an inducible promoter, a tissue-specific promoter, and a synthetic promoter.

18. An expression vector comprising the nucleic acid molecule of any one of claims 15-17.

19. The expression vector of claim 18, wherein the vector is a viral vector.

20. A cell comprising the chimeric protein of any one of claims 1-14, the nucleic acid molecule of any of claims 15-17, or the expression vector of any of claims 18-19.

21. The cell of claim 20, wherein the cell is selected from the group consisting of: a T cell, a CD8+ T cell, a CD4+ T cell, a gamma-delta T cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a viral-specific T cell, a Natural Killer T (NKT) cell, a Natural Killer (NK) cell, a B cell, a tumor-infiltrating lymphocyte (TIL), an innate lymphoid cell, a mast cell, an eosinophil, a basophil, a neutrophil, a myeloid cell, a macrophage, a monocyte, a dendritic cell, an erythrocyte, a platelet cell, a human embryonic stem cell (ESC), an ESC-derived cell, a pluripotent stem cell, a mesenchymal stromal cell (MSC), an induced pluripotent stem cell (iPSC), and an iPSC-derived cell.

22. The cell of any one of claims 20-21, wherein the cell further comprises a protease capable of cleaving the protease cleavage site.

23. The cell of claim 22, wherein the protease is an endogenous protease.

24. The cell of claim 20, wherein the membrane-cleavable chimeric protein is expressed in the cell and the effector molecule is tethered to a cell membrane of the cell.

25. The cell of claim 24, wherein the cell expresses a protease that cleaves the protease cleavage site and releases the effector molecule from the cell membrane.

26. A pharmaceutical composition comprising the membrane-cleavable chimeric protein of any one of claims 1-14, the nucleic acid of any one of claims 15-17, the expression vector of any one of claims 18-19, or the cell of any one of claims 20-25 and a pharmaceutically acceptable excipient.

27. The pharmaceutical composition of claim 26, wherein the pharmaceutical composition is a lipid nanoparticle pharmaceutical composition.

28. The pharmaceutical composition of any one of claims 26-27 for use as a medicament.

29. Use of the pharmaceutical composition of any one of claims 26-27 in the manufacture of a medicament for the treatment of a disease.

30. The use of claim 29, wherein the disease is cancer.