CLAIMS

WHAT IS CLAIMED IS:

1. A fusion protein comprising:
    (a) a first polypeptide subunit comprising the following elements in an N-to-C terminal orientation:
        i. a first mask polypeptide (Mask1),
        ii.a first linker (Linker1) comprising a first protease-cleavable release segment (RS1),
        iii. an IL-12 p35 polypeptide,
        iv. a second linker (Linker2) comprising a second protease-cleavable release segment (RS2), and
        v. a second mask polypeptide (Mask2); and
    (b) a second polypeptide subunit comprising the following elements in an N-to-C terminal orientation:
        i. a third mask polypeptide (Mask3),
        ii.a third linker (Linker3) comprising a third protease-cleavable release segment (RS3),
        iii. an IL-12 p40 polypeptide,
        iv. a fourth linker (Linker4) comprising a fourth protease-cleavable release segment (RS4), and
        v.a fourth mask polypeptide (Mask4);

wherein the IL-12 p35 polypeptide and the IL-12 p40 polypeptide are disulfide-linked;

wherein each release segment (RS1, RS2, RS3, and RS4) comprises the amino acid sequence of SEQ ID NO: 7628 (EAGRSAXHTPAGLTGP); and

wherein each mask polypeptide (Mask1, Mask2, Mask3, and Mark4) independently, has a length of 100 to 1000 amino acid residues and comprises a plurality of non-overlapping sequence motifs selected from GTSTEPSEGSAP (SEQ ID NO:189), GTSESATPESGP (SEQ ID NO:188), GSGPGTSESATP (SEQ ID NO:201), GSEPATSGSETP (SEQ ID NO:187), GSPAGSPTSTEE (SEQ ID NO:186), and GTSPSATPESGP (SEQ ID NO:202).

2. The fusion protein of claim 1, wherein the Mask1 comprises an amino sequence that has at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity, or 100% identity to SEQ ID NO: 8026.

3. The fusion protein of claim 1 or 2, wherein the Mask2 comprises an amino sequence that has at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity, or 100% identity to SEQ ID NO: 8028.

4. The fusion protein of any one of claims 1-3, wherein the Mask3 comprises an amino sequence that has at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity, or 100% identity to SEQ ID NO: 8023.

5. The fusion protein of any one of claims 1-4, wherein the Mask4 comprises an amino sequence that has at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity, or 100% identity to SEQ ID NO: 8025.

6. The fusion protein of any one of claims 1-5, wherein the IL-12 p35 polypeptide comprises the amino acid sequence of SEQ ID NO: 8050.

7. The fusion protein of any one of claims 1-5, wherein the IL-12 p35 polypeptide comprises the amino acid sequence of SEQ ID NO: 8055, wherein X is any amino acid residue other than asparagine (N).

8. The fusion protein of any one of claims 1-5, wherein the IL-12 p35 polypeptide comprises an amino acid sequence of SEQ ID NO: 8053

9. The fusion protein of any one of claims 1-8, wherein the IL-12 p40 polypeptide comprises the amino acid sequence of SEQ ID NO: 8051.

10. The fusion protein of claim 1, wherein the first polypeptide subunit comprises the amino acid sequence of SEQ ID NO: 1000, and wherein the second polypeptide subunit comprises the amino acid sequence of SEQ ID NO: 1033.

11. The fusion protein of claim 1, wherein the first polypeptide subunit comprises the amino acid sequence of SEQ ID NO: 1002, and wherein the second polypeptide subunit comprises the amino acid sequence of SEQ ID NO: 1033.

12. A polynucleotide sequence encoding the fusion protein of any one of claims 1-11.

13. An expression vector comprising the polynucleotide sequence of claim 12.

14. Use of the fusion protein of any one of claims 1-11 or the polynucleotide sequence of claim 12 in the manufacture of a medicament for treating cancer in a subject in need thereof.

15. The use of claim 14, wherein the cancer comprises a solid tumor.