

CLAIMS

1. A polypeptide complex comprising IL-12, a half-life extension element, an IL-12 blocking element and a protease cleavable linker, wherein the IL-12 blocking element is a single chain antibody the binds IL-12 or an antigen binding fragment thereof, and the complex comprises:
 - i. a first polypeptide comprising an IL-12 subunit, and optionally the IL-12 blocking element, wherein the IL-12 blocking element when present is operably linked to the IL-12 subunit through a first protease cleavable linker;
 - ii. a second polypeptide chain comprising an IL-12 subunit operably linked to a half-life extension element through a second protease cleavable linker, and optionally the IL-12 blocking element, wherein the IL-12 blocking element when present is operably linked to the IL-12 subunit through a first protease cleavable linker or is operably linked to the half-life extension element through a linker that is optionally protease cleavable;
wherein only one of the first and second polypeptide contains the IL-12 blocking element; and
wherein when the IL-12 subunit in the first polypeptide is p35 the IL-12 subunit in the second polypeptide is p40, and when the IL-12 subunit in the first polypeptide is p40 the IL-12 subunit in the second polypeptide is p35.
2. The polypeptide of claim 1, wherein the first protease cleavable linker and the second protease cleavable linker are the same.
3. A polypeptide complex comprising IL-12, a half-life extension element, an IL-12 blocking element and a protease cleavable linker, wherein the IL-12 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen-binding portion of an antibody light chain and at least an antigen-binding portion of a complementary antibody heavy chain, and the complex comprises:

- i. a first polypeptide comprising an IL-12 subunit, and optionally a half-life extension element, wherein the half-life extension element when present is operably linked to the IL-12 subunit through a first protease cleavable linker;
 - ii. a second polypeptide comprising an IL -12 subunit, at least an antigen binding portion of an antibody light chain or an antigen binding portion of an antibody heavy chain, and optionally a half-life extension element; wherein when the half-life extension element is present it is operably linked to the IL-12 subunit through a first protease cleavable linker and the antibody heavy chain or light chain is either a) operably linked to the IL-12 subunit through a second protease cleavable linker, or b) operably linked to the half-life extension element through an optionally cleavable linker; and
 - iii. a third polypeptide comprising at least an antigen binding portion of an antibody heavy chain that is complementary to the light chain in the second polypeptide, or an antibody light chain that is complementary to the heavy chain in the second polypeptide and together with said light chain forms and IL-12 binding site; wherein when the IL-12 subunit in the first polypeptide is p35 the IL-12 subunit in the second polypeptide is p40, and when the IL-12 subunit in the first polypeptide is p40 the IL-12 subunit in the second polypeptide is p35.
4. The polypeptide of claim 3, wherein the first protease cleavable linker and the second protease cleavable linker are the same.
5. A polypeptide complex comprising IL-12, a half-life extension element, an IL-12 blocking element and a protease cleavable linker, wherein the IL-12 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen binding portion of an antibody light chain and at least an antigen binding portion of a complementary antibody heavy chain, and the complex comprises:
- i. a first polypeptide chain comprising p35, p40, a half-life extension element and at least an antigen binding portion of an antibody light chain, wherein p35 and p40 are operably linked, and the half-life extension element is operably linked to p40 through a first protease cleavable linker and the antigen binding portion of an antibody light chain is operably linked to p35 through a second protease cleavable linker; or the half-

- life extension element is operably linked to p35 through a first protease cleavable linker and the antigen binding portion of an antibody light chain is operably linked to p40 through a second protease cleavable linker; and
- ii. a second polypeptide that comprises at least an antigen binding portion of an antibody heavy chain that is complementary to the light chain in the second polypeptide and together with said light chain forms and IL-12 binding site.
6. A polypeptide complex comprising IL-12, a half-life extension element, an IL-12 blocking element and a protease cleavable linker, wherein the IL-12 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen binding portion of an antibody light chain and at least an antigen binding portion of a complementary antibody heavy chain, and the complex comprises:
- iii. a first polypeptide chain comprising p35, p40, a half-life extension element and at least an antigen binding portion of an antibody heavy chain, wherein p35 and p40 are operably linked, and the half-life extension element is operably linked to p40 through a first protease cleavable linker and the antigen binding portion of an antibody heavy chain is operably linked to p35 through a second protease cleavable linker; or the half-life extension element is operably linked to p35 through a first protease cleavable linker and the antigen binding portion of an antibody heavy chain is operably linked to p40 through a second protease cleavable linker; and
 - iv. a second polypeptide that comprises at least an antigen binding portion of an antibody light chain that is complementary to the heavy chain in the second polypeptide and together with said light chain forms and IL-12 binding site.
7. The polypeptide of claim 5 or 6, wherein the first protease cleavable linker and the second protease cleavable linker are the same.
8. The polypeptide complex as in claim 1 or 3, wherein the first polypeptide does not comprise a blocking element and the second polypeptide has the formula:
 [A]-[L1]-[B]-[L3]-[D] or [D]-[L3]-[B]-[L1]-[A] or [B]-[L1]-[A]-[L2]-[D] or [D]-[L1]-[A]-[L2]-[B], wherein,

A is the IL-12 subunit;

L1 is the first protease-cleavable linker;

L2 is the second protease cleavable linker;

L3 is the optionally cleavable linker;

B is the half-life extension element; and

D is the blocking element.

9. The polypeptide complex of claim 1, wherein the first polypeptide comprises the formula:

[A]-[L1]-[D] or [D]-[L1]-[A]; and the second polypeptide has the formula:

[A']-[L2]-[B] or [B]-[L2]-[A'], wherein

A is either p35 or p40, wherein when A is p35, A' is p40 and when A is p40, A' is p35;

A' is either p35 or p40;

L1 is the first protease cleavable linker;

L2 is the second protease cleavable linker;

B is the half-life extension element; and

D is the blocking element.

10. The polypeptide complex of claim 3, wherein the first polypeptide comprises the formula:

[A]-[L1]-[B] or [B]-[L1]-[A]; and the second polypeptide has the formula [A']-[L2]-[D] or [D]-[L2]-[A'], wherein

A is either p35 or p40;

A' is either p35 or p40, wherein when A is p35, A' is p40 and when A is p40, A' is p35;

L1 is the first protease cleavable linker;

L2 is the second protease cleavable linker;

B is the half-life extension element; and

D is the blocking element.

11. The polypeptide complex of any one of claims 1-10, wherein the half-life extension element is a human serum albumin, an antigen binding polypeptide that binds human serum albumin, or an immunoglobulin Fc or fragment thereof.
12. The polypeptide complex of any one of claims 1-10, wherein the protease cleavable linker comprises a sequence that is capable of being cleaved by a protease selected from kallikrein, thrombin, chymase, carboxypeptidase A, cathepsin, elastase, PR-3, granzyme M, a calpain, a matrix metalloproteinase (MMP), an ADAM, a FAP, a plasminogen activator, a caspase, a tryptase, or a tumor protease.
13. The polypeptide complex of any one of claims 1-10, wherein the protease is selected from cathepsin B, cathepsin C, cathepsin D, cathepsin E, cathepsin K, cathepsin L, or cathepsin G.
14. The polypeptide complex of any one of claims 1-10, wherein protease is selected from matrix metalloprotease (MMP) is MMP1, MMP2, MMP3, MMP8, MMP9, MMP10, MMP11, MMP12, MMP13, or MMP14.
15. The polypeptide complex of any one of claims 1-10, wherein the protease cleavable linker comprises at least two sequences that are independently capable of being cleaved by a protease.
16. The polypeptide complex of any one of claims 1-10, wherein the protease cleavable linker comprises a synthetic sequence.
17. The polypeptide complex of any one of the preceding claims, wherein each of the protease cleavable linkers are cleaved by two or more different proteases.
18. The polypeptide complex of claim 1, wherein the single chain antibody is a single chain variable fragment (scFv).

19. The polypeptide complex as in claim 3, 5 or 6, wherein the antigen binding fragment of an antibody is a Fab.
20. The polypeptide complex of any one of claims 1, 3, 5, or 6, wherein the blocking element binds the IL-12.
21. The polypeptide complex of claim 17 or 18, wherein the blocking element binds p35, p40, or to the p35p40 complex.
22. A nucleic acid encoding a polypeptides as defined in any one of claims 1-21.
23. The nucleic acid of claim 22, wherein the nucleic acid does not encode only p35 or p40.
24. A nucleic acid composition comprising one or more nucleic acid sequences encoding a polypeptide complex comprising IL-12, a half-life extension element, an IL-12 blocking element and a protease cleavable linker, wherein the IL-12 blocking element is a single chain antibody the binds IL-12 or an antigen binding fragment thereof, and the complex comprises:
 - iii. a first polypeptide comprising an IL-12 subunit, and optionally the IL-12 blocking element, wherein the IL-12 blocking element when present is operably linked to the IL-12 subunit through a first protease cleavable linker;
 - iv. a second polypeptide chain comprising an IL-12 subunit operably linked to a half-life extension element through a second protease cleavable linker, and optionally the IL-12 blocking element, wherein the IL-12 blocking element when present is operably linked to the IL-12 subunit through a first protease cleavable linker or is operably linked to the half-life extension element through a linker that is optionally protease cleavable;wherein only one of the first and second polypeptide contains the IL-12 blocking element; and

wherein when the IL-12 subunit in the first polypeptide is p35 the IL-12 subunit in the second polypeptide is p40, and when the IL-12 subunit in the first polypeptide is p40 the IL-12 subunit in the second polypeptide is p35.

25. A nucleic acid composition comprising one or more nucleic acid sequences encoding a polypeptide complex comprising IL-12, a half-life extension element, an IL-12 blocking element and a protease cleavable linker, wherein the IL-12 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen-binding portion of an antibody light chain and at least an antigen-binding portion of the a complementary antibody heavy chain, and the complex comprises:

- i. a first polypeptide comprising an IL-12 subunit, and optionally a half-life extension element, wherein the half-life extension element when present is operably linked to the IL-12 subunit through a first protease cleavable linker;
- ii. a second polypeptide comprising an IL -12 subunit, at least an antigen binding portion of an antibody light chain, and optionally a half-life extension element; wherein when the half-life extension element is present it is operably linked to the IL-12 subunit through a first protease cleavable linker and the antibody heavy chain or light chain is either a) operably linked to the IL-12 subunit through a second protease cleavable linker, or b) operably linked to the half-life extension element through an optionally cleavable linker; and
- iii. a third polypeptide comprising at least an antigen binding portion of an antibody heavy chain that is complementary to the light chain in the second polypeptide and together with said light chain forms and IL-12 binding site;

wherein when the IL-12 subunit in the first polypeptide is p35 the IL-12 subunit in the second polypeptide is p40, and when the IL-12 subunit in the first polypeptide is p40 the IL-12 subunit in the second polypeptide is p35.

26. A nucleic acid composition comprising one or more nucleic acid sequences encoding a polypeptide complex comprising IL-12, a half-life extension element, an IL-12 blocking element and a protease cleavable linker, wherein the IL-12 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen binding portion of an antibody light chain and at least an antigen binding portion of a complementary antibody heavy chain, and the complex comprises:

- i. a first polypeptide chain comprising p35, p40, a half-life extension element and at least an antigen binding portion of an antibody light chain, wherein p35 and p40 are operably linked, and the half-life extension element is operably linked to p40 through a first protease cleavable linker and the antigen binding portion of an antibody light chain is operably linked to p35 through a second protease cleavable linker; or the half-life extension element is operably linked to p35 through a first protease cleavable linker and the antigen binding portion of an antibody light chain is operably linked to p40 through a second protease cleavable linker; and
 - ii. a second polypeptide that comprises at least an antigen binding portion of an antibody heavy chain that is complementary to the light chain in the second polypeptide and together with said light chain forms and IL-12 binding site.
27. A nucleic acid composition comprising one or more nucleic acid sequences encoding a polypeptide complex comprising IL-12, a half-life extension element, an IL-12 blocking element and a protease cleavable linker, wherein the IL-12 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen binding portion of an antibody light chain and at least an antigen binding portion of a complementary antibody heavy chain, and the complex comprises:
- iii. a first polypeptide chain comprising p35, p40, a half-life extension element and at least an antigen binding portion of an antibody heavy chain, wherein p35 and p40 are operably linked, and the half-life extension element is operably linked to p40 through a first protease cleavable linker and the antigen binding portion of an antibody heavy chain is operably linked to p35 through a second protease cleavable linker; or the half-life extension element is operably linked to p35 through a first protease cleavable linker and the antigen binding portion of an antibody heavy chain is operably linked to p40 through a second protease cleavable linker; and
 - iv. a second polypeptide that comprises at least an antigen binding portion of an antibody light chain that is complementary to the heavy chain in the second polypeptide and together with said heavy chain forms and IL-12 binding site.
28. The nucleic acid composition of any one of claims 22-27, comprising a circular vector.

29. The nucleic acid composition of any one of claims 22-27, comprising DNA.
30. The nucleic acid composition of any one of claims 22-27, comprising RNA.
31. An expression vector comprising the nucleic acid of any one of claims 22-27.
32. An isolated host cell comprising the vector of claim 31.
33. A method of making a pharmaceutical composition, comprising culturing the isolated host cell of claim 32 under suitable conditions for expression of the polypeptide complex.
34. The method of claim 33, further comprising isolating the polypeptide complex.
35. A pharmaceutical composition comprising a protein complex of any one of claims 1-21 or nucleic acid of any one of claims 22-31.
36. ~~Use of A method for treating a tumor, comprising administering to a subject in need thereof~~ an effective amount of the polypeptide complex of any one of claims 1-21, a nucleic acid of any one of claims 22-30, the expression vector of claim 31, or the pharmaceutical composition of claim 34 in the manufacture of a medicament for treating a tumor in a subject in need thereof.
37. An IL-12 polypeptide complex comprising a first polypeptide selected from the group consisting of SEQ ID NOs: 95-110, SEQ ID NOs: 119-126, and SEQ ID NOs: 135-143, or an amino acid sequence that has at least 80% identity to SEQ ID NOs: 95-110, SEQ ID NOs: 119-126, and SEQ ID NOs: 135-143.
38. An IL-12 polypeptide complex comprising a first polypeptide comprising SEQ ID NO: 104 or SEQ ID NO: 136.

39. An IL-12 polypeptide complex comprising a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 104 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 18.
40. A polypeptide complex comprising a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 136 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 18.
41. A single chain IL-12 inducible polypeptide comprising the amino acid selected from the group consisting of SEQ ID NOs: 7, 9, 10, 18, 24-94, SEQ ID NOs: 110-118, and SEQ ID NOs: 127-134, or an amino acid sequence that has at least about 80% identity to SEQ ID NOs: 7, 9, 10, 18, 24-94, SEQ ID NOs: 110-118, and SEQ ID NOs: 127-134.
42. An inducible IL-12 polypeptide comprising p35, p40, a blocking element and a half-life extension element, wherein the blocking element is an antibody or an antigen binding fragment that has binding specificity for the epitope on IL-12 defined by the amino acids in Table 1.
43. A nucleic acid encoding a polypeptide as defined in any one of claims 37-42.
44. The nucleic acid composition of any one of claims 37-42, comprising a circular vector.
45. The nucleic acid composition of any one of claims 37-42, comprising DNA.
46. The nucleic acid composition of any one of claims 37-42, comprising RNA.
47. An expression vector comprising the nucleic acid of any one of claims 37-42.
48. An isolated host cell comprising the vector of claim 47.
49. A method of making a pharmaceutical composition, comprising culturing the isolated host cell of claim 48 under suitable conditions for expression of the polypeptide complex.

50. The method of claim 49, further comprising isolating the polypeptide complex.
51. A pharmaceutical composition comprising a protein complex of any one of claims 37-40 or 42, or a polypeptide of claim 41, or nucleic acid of any one of claims 43-47.
52. ~~A method for treating a tumor, comprising administering to a subject in need thereof~~ Use of an effective amount of the polypeptide complex of any one of claims 37-40 or 42, a nucleic acid of any one of claims 43-47, the expression vector of claim 48, or the pharmaceutical composition of claim 51 in the manufacture of a medicament for treating a tumor in a subject in need thereof.
53. The polypeptide of any one of claims 1-10 or the nucleic acid composition of any one of claims 24-27, wherein the IL-12 is a mutein.
54. The polypeptide of claim 53 or the nucleic acid composition of claim 53, wherein the IL-12 is partially or fully aglycosylated.
55. The polypeptide of claim 54 or the nucleic acid composition of claim 54, wherein the p35 and/or p40 is partially or fully aglycosylated.
56. The polypeptide of claim 55 or the nucleic acid composition of claim 55, wherein the p35 and/or p40 is fully aglycosylated.
57. A polypeptide complex comprising IL-23, a half-life extension element, an IL-23 blocking element and a protease cleavable linker, wherein the IL-23 blocking element is a single chain antibody the binds IL-23 or an antigen binding fragment thereof, and the complex comprises:
- v. a first polypeptide comprising an IL-23 subunit, and optionally the IL-23 blocking element, wherein the IL-23 blocking element when present is operably linked to the IL-23 subunit through a first protease cleavable linker;

- vi. a second polypeptide chain comprising an IL-23 subunit operably linked to a half-life extension element through a second protease cleavable linker, and optionally the IL-23 blocking element, wherein the IL-23 blocking element when present is operably linked to the IL-23 subunit through a first protease cleavable linker or is operably linked to the half-life extension element through a linker that is optionally protease cleavable;

wherein only one of the first and second polypeptide contains the IL-23 blocking element; and

wherein when the IL-23 subunit in the first polypeptide is p19 the IL-23 subunit in the second polypeptide is p40, and when the IL-23 subunit in the first polypeptide is p40 the IL-23 subunit in the second polypeptide is p19.

58. The polypeptide of claim 57, wherein the first protease cleavable linker and the second protease cleavable linker are the same.

59. A polypeptide complex comprising IL-23, a half-life extension element, an IL-23 blocking element and a protease cleavable linker, wherein the IL-23 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen-binding portion of an antibody light chain and at least an antigen-binding portion of a complementary antibody heavy chain, and the complex comprises:

- iv. a first polypeptide comprising an IL-23 subunit, and optionally a half-life extension element, wherein the half-life extension element when present is operably linked to the IL-23 subunit through a first protease cleavable linker;
- v. a second polypeptide comprising an IL -12 subunit, at least an antigen binding portion of an antibody light chain or an antigen binding portion of an antibody heavy chain, and optionally a half-life extension element; wherein when the half-life extension element is present it is operably linked to the IL-23 subunit through a first protease cleavable linker and the antibody heavy chain or light chain is either a) operably linked to the IL-23 subunit through a second protease cleavable linker, or b) operably linked to the half-life extension element through an optionally cleavable linker; and
- vi. a third polypeptide comprising at least an antigen binding portion of an antibody heavy chain that is complementary to the light chain in the second polypeptide, or an

antibody light chain that is complementary to the heavy chain in the second polypeptide and together with said light chain forms and IL-23 binding site;

wherein when the IL-23 subunit in the first polypeptide is p19 the IL-23 subunit in the second polypeptide is p40, and when the IL-23 subunit in the first polypeptide is p40 the IL-23 subunit in the second polypeptide is p19.

60. The polypeptide of claim 59, wherein the first protease cleavable linker and the second protease cleavable linker are the same.

61. A polypeptide complex comprising IL-23, a half-life extension element, an IL-23 blocking element and a protease cleavable linker, wherein the IL-23 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen binding portion of an antibody light chain and at least an antigen binding portion of a complementary antibody heavy chain, and the complex comprises:

- v. a first polypeptide chain comprising p19, p40, a half-life extension element and at least an antigen binding portion of an antibody light chain, wherein p19 and p40 are operably linked, and the half-life extension element is operably linked to p40 through a first protease cleavable linker and the antigen binding portion of an antibody light chain is operably linked to p19 through a second protease cleavable linker; or the half-life extension element is operably linked to p19 through a first protease cleavable linker and the antigen binding portion of an antibody light chain is operably linked to p40 through a second protease cleavable linker; and
- vi. a second polypeptide that comprises at least an antigen binding portion of an antibody heavy chain that is complementary to the light chain in the second polypeptide and together with said light chain forms and IL-23 binding site.

62. A polypeptide complex comprising IL-23, a half-life extension element, an IL-23 blocking element and a protease cleavable linker, wherein the IL-23 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen binding portion of an antibody

light chain and at least an antigen binding portion of a complementary antibody heavy chain, and the complex comprises:

- vii. a first polypeptide chain comprising p19, p40, a half-life extension element and at least an antigen binding portion of an antibody heavy chain, wherein p19 and p40 are operably linked, and the half-life extension element is operably linked to p40 through a first protease cleavable linker and the antigen binding portion of an antibody heavy chain is operably linked to p19 through a second protease cleavable linker; or the half-life extension element is operably linked to p19 through a first protease cleavable linker and the antigen binding portion of an antibody heavy chain is operably linked to p40 through a second protease cleavable linker; and
- viii. a second polypeptide that comprises at least an antigen binding portion of an antibody light chain that is complementary to the heavy chain in the second polypeptide and together with said light chain forms and IL-23 binding site.

63. The polypeptide of claim 61 or 62, wherein the first protease cleavable linker and the second protease cleavable linker are the same.

64. The polypeptide complex as in claim 57 or 59, wherein the first polypeptide does not comprise a blocking element and the second polypeptide has the formula:

[A]-[L1]-[B]-[L3]-[D] or [D]-[L3]-[B]-[L1]-[A] or [B]-[L1]-[A]-[L2]-[D] or [D]-[L1]-[A]-[L2]-[B], wherein,

A is the IL-23 subunit;

L1 is the first protease-cleavable linker;

L2 is the second protease cleavable linker;

L3 is the optionally cleavable linker;

B is the half-life extension element; and

D is the blocking element.

65. The polypeptide complex of claim 57, wherein the first polypeptide comprises the formula:

[A]-[L1]-[D] or [D]-[L1]-[A]; and the second polypeptide has the formula:

[A']-[L2]-[B] or [B]-[L2]-[A'], wherein

A is either p19 or p40, wherein when A is p19, A' is p40 and when A is p40, A' is p19;
A' is either p19 or p40;

L1 is the first protease cleavable linker;

L2 is the second protease cleavable linker;

B is the half-life extension element; and

D is the blocking element.

66. The polypeptide complex of claim 59, wherein the first polypeptide comprises the formula: [A]-[L1]-[B] or [B]-[L1]-[A]; and the second polypeptide has the formula [A']-[L2]-[D] or [D]-[L2]-[A'], wherein

A is either p19 or p40;

A' is either p19 or p40, wherein when A is p19, A' is p40 and when A is p40, A' is p19;

L1 is the first protease cleavable linker;

L2 is the second protease cleavable linker;

B is the half-life extension element; and

D is the blocking element.

67. The polypeptide complex of any one of claims 57-66, wherein the half-life extension element is a human serum albumin, an antigen binding polypeptide that binds human serum albumin, or an immunoglobulin Fc or fragment thereof.

68. The polypeptide complex of any one of claims 57-66, wherein the protease cleavable linker comprises a sequence that is capable of being cleaved by a protease selected from kallikrein, thrombin, chymase, carboxypeptidase A, cathepsin, elastase, PR-3, granzyme M, a calpain, a matrix metalloproteinase (MMP), an ADAM, a FAP, a plasminogen activator, a caspase, a tryptase, or a tumor protease.

69. The polypeptide complex of any one of claims 57-66, wherein the protease is selected from cathepsin B, cathepsin C, cathepsin D, cathepsin E, cathepsin K, cathepsin L, or cathepsin G.
70. The polypeptide complex of any one of claims 57-66, wherein protease is selected from matrix metalloprotease (MMP) is MMP1, MMP2, MMP3, MMP8, MMP9, MMP10, MMP11, MMP12, MMP13, or MMP14.
71. The polypeptide complex of any one of claims 57-66, wherein the protease cleavable linker comprises at least two sequences that are independently capable of being cleaved by a protease.
72. The polypeptide complex of any one of claims 57-66, wherein the protease cleavable linker comprises a synthetic sequence.
73. The polypeptide complex of any one of the preceding claims, wherein each of the protease cleavable linkers are cleaved by two or more different proteases.
74. The polypeptide complex of claim 57, wherein the single chain antibody is a single chain variable fragment (scFv).
75. The polypeptide complex as in claim 59, 61 or 62, wherein the antigen binding fragment of an antibody is a Fab.
76. The polypeptide complex of any one of claims 57, 59, 61, or 62, wherein the blocking element binds the IL-23.
77. The polypeptide complex of claim 73 or 74, wherein the blocking element binds p19, p40, or to the p19p40 complex.
78. A nucleic acid encoding a polypeptides as defined in any one of claims 57-77.

79. The nucleic acid of claim 78, wherein the nucleic acid does not encode only p19 or p40.

80. A nucleic acid composition comprising one or more nucleic acid sequences encoding a polypeptide complex comprising IL-23, a half-life extension element, an IL-23 blocking element and a protease cleavable linker, wherein the IL-23 blocking element is a single chain antibody the binds IL-23 or an antigen binding fragment thereof, and the complex comprises:

- vii. a first polypeptide comprising an IL-23 subunit, and optionally the IL-23 blocking element, wherein the IL-23 blocking element when present is operably linked to the IL-23 subunit through a first protease cleavable linker;
- viii. a second polypeptide chain comprising an IL-23 subunit operably linked to a half-life extension element through a second protease cleavable linker, and optionally the IL-23 blocking element, wherein the IL-23 blocking element when present is operably linked to the IL-23 subunit through a first protease cleavable linker or is operably linked to the half-life extension element through a linker that is optionally protease cleavable;

wherein only one of the first and second polypeptide contains the IL-23 blocking element; and

wherein when the IL-23 subunit in the first polypeptide is p19 the IL-23 subunit in the second polypeptide is p40, and when the IL-23 subunit in the first polypeptide is p40 the IL-23 subunit in the second polypeptide is p19.

81. A nucleic acid composition comprising one or more nucleic acid sequences encoding a polypeptide complex comprising IL-23, a half-life extension element, an IL-23 blocking element and a protease cleavable linker, wherein the IL-23 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen-binding portion of an antibody light chain and at least an antigen-binding portion of the a complementary antibody heavy chain, and the complex comprises:

- iv. a first polypeptide comprising an IL-23 subunit, and optionally a half-life extension element, wherein the half-life extension element when present is operably linked to the IL-23 subunit through a first protease cleavable linker;

- v. a second polypeptide comprising an IL -12 subunit, at least an antigen binding portion of an antibody light chain, and optionally a half-life extension element; wherein when the half-life extension element is present it is operably linked to the IL-23 subunit through a first protease cleavable linker and the antibody heavy chain or light chain is either a) operably linked to the IL-23 subunit through a second protease cleavable linker, or b) operably linked to the half-life extension element through an optionally cleavable linker; and
 - vi. a third polypeptide comprising at least an antigen binding portion of an antibody heavy chain that is complementary to the light chain in the second polypeptide and together with said light chain forms and IL-23 binding site;
wherein when the IL-23 subunit in the first polypeptide is p19 the IL-23 subunit in the second polypeptide is p40, and when the IL-23 subunit in the first polypeptide is p40 the IL-23 subunit in the second polypeptide is p19.
82. A nucleic acid composition comprising one or more nucleic acid sequences encoding a polypeptide complex comprising IL-23, a half-life extension element, an IL-23 blocking element and a protease cleavable linker, wherein the IL-23 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen binding portion of an antibody light chain and at least an antigen binding portion of a complementary antibody heavy chain, and the complex comprises:
- v. a first polypeptide chain comprising p19, p40, a half-life extension element and at least an antigen binding portion of an antibody light chain, wherein p19 and p40 are operably linked, and the half-life extension element is operably linked to p40 through a first protease cleavable linker and the antigen binding portion of an antibody light chain is operably linked to p19 through a second protease cleavable linker; or the half-life extension element is operably linked to p19 through a first protease cleavable linker and the antigen binding portion of an antibody light chain is operably linked to p40 through a second protease cleavable linker; and
 - vi. a second polypeptide that comprises at least an antigen binding portion of an antibody heavy chain that is complementary to the light chain in the second polypeptide and together with said light chain forms and IL-23 binding site.

83. A nucleic acid composition comprising one or more nucleic acid sequences encoding a polypeptide complex comprising IL-23, a half-life extension element, an IL-23 blocking element and a protease cleavable linker, wherein the IL-23 blocking element is an antigen binding fragment of an antibody, wherein the antigen binding fragment comprises as separate components, at least an antigen binding portion of an antibody light chain and at least an antigen binding portion of a complementary antibody heavy chain, and the complex comprises:
- vii. a first polypeptide chain comprising p19, p40, a half-life extension element and at least an antigen binding portion of an antibody heavy chain, wherein p19 and p40 are operably linked, and the half-life extension element is operably linked to p40 through a first protease cleavable linker and the antigen binding portion of an antibody heavy chain is operably linked to p19 through a second protease cleavable linker; or the half-life extension element is operably linked to p19 through a first protease cleavable linker and the antigen binding portion of an antibody heavy chain is operably linked to p40 through a second protease cleavable linker; and
 - viii. a second polypeptide that comprises at least an antigen binding portion of an antibody light chain that is complementary to the heavy chain in the second polypeptide and together with said heavy chain forms and IL-23 binding site.
84. The nucleic acid composition of any one of claims 78-83, comprising a circular vector.
85. The nucleic acid composition of any one of claims 78-83, comprising DNA.
86. The nucleic acid composition of any one of claims 78-83, comprising RNA.
87. An expression vector comprising the nucleic acid of any one of claims 78-83.
88. An isolated host cell comprising the vector of claim 87.
89. A method of making a pharmaceutical composition, comprising culturing the isolated host cell of claim 88 under suitable conditions for expression of the polypeptide complex.

90. The method of claim 89, further comprising isolating the polypeptide complex.
91. A pharmaceutical composition comprising a protein complex of any one of claims 57-77 or nucleic acid of any one of claims 78-86.
92. ~~A method for treating a tumor, comprising administering to a subject in need thereof~~ Use of an effective amount of the polypeptide complex of any one of claims 57-77, a nucleic acid of any one of claims 78-86, the expression vector of claim 87, or the pharmaceutical composition of claim 91 in the manufacture of a medicament for treating a tumor in a subject in need thereof.
93. An IL-23 polypeptide complex comprising a first polypeptide selected from the group consisting of SEQ ID NOs: 423-428, or an amino acid sequence that has at least 80% identity to SEQ ID NOs: 423-428.
94. The IL-23 polypeptide complex of claim 93, further comprising a second polypeptide chain comprising the amino acid sequence of SEQ ID NOs: 104, 434 or 442-445 or an amino acid sequence that has at least 80% identity to SEQ ID NOs: 104, 434 or 442-445.
95. A single chain IL-23 inducible polypeptide comprising the amino acid selected from the group consisting of SEQ ID NOs: 422 or 429-432, or an amino acid sequence that has at least about 80% identity to SEQ ID NOs: 422 or 429-432.
96. An inducible IL-23 polypeptide comprising p19, p40, a blocking element and a half-life extension element, wherein the blocking element is an antibody or an antigen binding fragment that has binding specificity for the epitope on IL-23.
97. A nucleic acid encoding a polypeptide as defined in any one of claims 93-96.
98. The nucleic acid composition of any one of claims 93-97, comprising a circular vector.

99. The nucleic acid composition of any one of claims 93-98, comprising DNA.
100. The nucleic acid composition of any one of claims 93-98, comprising RNA.
101. An expression vector comprising the nucleic acid of any one of claims 97-100.
102. An isolated host cell comprising the vector of claim 101.
103. A method of making a pharmaceutical composition, comprising culturing the isolated host cell of claim 102 under suitable conditions for expression of the polypeptide complex.
104. The method of claim 103, further comprising isolating the polypeptide complex.
105. A pharmaceutical composition comprising a polypeptide complex of any one of claims 93-96, or nucleic acid of any one of claims 97-100.
106. ~~A method for treating a tumor, comprising administering to a subject in need thereof~~
Use of an effective amount of the polypeptide complex of any one of claims 93-96, a nucleic acid of any one of claims 97-100, the expression vector of claim 101, or the pharmaceutical composition of claim 105 in the manufacture of a medicament for treating a tumor in a subject in need thereof.
107. The polypeptide of any one of claims 57-66 or the nucleic acid composition of any one of claims 80-86, wherein the IL-23 is a mutein.
108. The polypeptide of claim 53 or the nucleic acid composition of claim 107, wherein the IL-23 is partially or fully aglycosylated.
109. The polypeptide of claim 108 or the nucleic acid composition of claim 108, wherein the p19 and/or p40 is partially or fully aglycosylated.

110. The polypeptide of claim 109 or the nucleic acid composition of claim 109, wherein the p19 and/or p40 is fully aglycosylated.