WHAT IS CLAIMED IS:

1. An activatable cytokine construct (ACC) that includes a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1),

wherein the CM1 is positioned between the CP1 and the DD1; and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2),

wherein the CM2 is positioned between the CP2 and the DD2; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first dimerization domain (DD1), and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a cleavable moiety (CM), and a second dimerization domain (DD2), wherein the CM is positioned between the CP2 and the DD2, wherein the CM functions as a substrate for a protease; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a cleavable moiety (CM), and a first dimerization domain (DD1), wherein the CM is positioned between the CP1 and the DD1, and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), and a second dimerization domain (DD2),

wherein the CM functions as a substrate for a protease; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), and a first dimerization domain (DD1), and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), and a second dimerization domain (DD2), wherein the CP1, the CP2, or both CP1 and CP2 include(s) an amino acid sequence that functions as a substrate for a protease;

further wherein (c) the DD1 and the DD2 bind each other thereby forming a dimer of the first monomer construct and the second monomer construct; and

further wherein (d) the ACC is characterized by having a reduced level of at least one CP1 and/or CP2 activity as compared to a control level of the at least one CP1 and/or CP2 activity.

2. The ACC of claim 1, wherein the first monomer construct comprises a first polypeptide that comprises the CP1, the CM1, and the DD1.

3. The ACC of any one or combination of claim 1 or 2, wherein the second monomer construct comprises a second polypeptide that comprises the CP2, the CM2, and the DD2.

4. The ACC of any one or combination of claims 1-3, wherein the DD1 and the DD2 are a pair selected from the group consisting of: a pair of Fc domains, a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα) and a soluble IL-15; barnase and barnstar; a PKA and an AKAP; adapter/docking tag modules based on mutated RNase I fragments; an epitope and sdAb; an epitope and scFv; and SNARE modules based on interactions of the proteins syntaxin, synaptotagmin, synaptobrevin, and SNAP25, an antigen-binding domain and an epitope.

5. The ACC of claim 4, wherein the DD1 and the DD2 are a pair of Fc domains.

6. The ACC of claim 5, wherein the pair of Fc domains is a pair of human Fc domains.

7. The ACC of claim 6, wherein the human Fc domains are human IgG1 Fc domains, human IgG2 Fc domains, human IgG3 Fc domains, or human IgG4 Fc domains.

8. The ACC of claim 7, wherein the human Fc domains are human IgG4 Fc domains.

9. The ACC of claim 8, wherein the human Fc domains comprise a sequence that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 3, SEQ ID NO: 315, or SEQ ID NO: 316.

10. The ACC of claim 9, wherein the human Fc domains comprise a sequence that is at least 90% identical to SEQ ID NO: 3, SEQ ID NO: 315, or SEQ ID NO: 316.

11. The ACC of claim 10, wherein the human Fc domains comprise SEQ ID NO: 3, SEQ ID NO: 315, or SEQ ID NO: 316.

12. The ACC of any one or combination of claims 1-3 and 5-11, wherein the DD1 and the DD2 are the same.

13. The ACC of claim 4, wherein DD1 comprises an antigen-binding domain and DD2 comprises a corresponding epitope.

14. The ACC of claim 13, wherein the antigen-binding domain is an anti-His tag antigen-binding domain and wherein the DD2 comprises a His tag.

15. The ACC of claim 13, wherein the antigen-binding domain is a single chain variable fragment (scFv).

16. The ACC of claim 13, wherein the antigen-binding domain is a single domain antibody (sdAb).

17. The ACC of claim 1, wherein at least one of DD1 and DD2 comprises a dimerization domain substituent selected from the group consisting of a non-polypeptide polymer and a small molecule.

18. The ACC of claim 17, wherein DD1 and DD2 comprise non-polypeptide polymers covalently bound to each other.

19. The ACC of claim 18, wherein the non-polypeptide polymer is a sulfur-containing polyethylene glycol, and wherein DD1 and DD2 are covalently bound to each other via one or more disulfide bonds.

20. The ACC of claim 17, wherein at least one of DD1 and DD2 comprises a small molecule.

21. The ACC of claim 20, wherein the small molecule is biotin.

22. The ACC of claim 20, wherein DD1 comprises biotin and DD2 comprises an avidin.

23. The ACC of any one or combination of claims 1-22, wherein the CP1 and/or the CP2 is/are each individually selected from the group consisting of: an interferon, an interleukin, GM-CSF, G-CSF, LIF, OSM, CD154, LT-β, TNF-α, TNF-β, 4-1BBL, APRIL, CD70, CD153, CD178, GITRL, LIGHT, OX40L, TALL-1, TRAIL, TWEAK, TRANCE, TGF-β1, TGF-β1, TGF-β3, Epo, Tpo, Flt-3L, SCF, M-CSF, and MSP.

24. The ACC of any one or combination of claims 1-23, wherein the CP1 and the CP2 are the same.

25. The ACC of any one or combination of claims 1-23 wherein the CP1 and the CP2 are different.

26. The ACC of any one or combination of claims 1-23, wherein the CP1 and/or the CP2 is/are an interferon.

27. The ACC of claim 26, wherein the CP1 and the CP2 are an interferon.

28. The ACC of claim 26, wherein the CP1 and the CP2 are different interferons.

29. The ACC of claim 26, wherein the CP1 and the CP2 are the same interferon.

30. The ACC of claim 26, wherein the CP1 or the CP2 is an interferon.

31. The ACC of any one or combination of claims 26-30, wherein the interferon(s) is/are a human wildtype mature interferon.

32. The ACC of any one or combination of claims 26-31, wherein the interferon(s) is/are selected from the group consisting of: interferon-alpha, interferon-beta, interferon-omega, and interferon-tau.

33. The ACC of claim 32, wherein the interferons is/are an interferon-alpha.

34. The ACC of claim 33, wherein the interferon(s) is/are selected from the group consisting of: interferon alpha-2a, interferon alpha-2b, and interferon alpha-n3.

35. The ACC of claim 34, wherein the interferon(s) is/are interferon alpha-2b.

36. The ACC of claim 35, wherein the CP1 and/or CP2 comprises a sequence that is at least 80% identical to SEQ ID NO: 1.

37. The ACC of claim 36, wherein the CP1 and/or CP2 comprises a sequence that is at least 90% identical to SEQ ID NO: 1.

38. The ACC of claim 37, wherein the CP1 and/or CP2 comprises a sequence of SEQ ID NO: 1.

39. The ACC of claim 32, wherein the interferon is an interferon beta.

40. The ACC of claim 39, wherein the interferon beta is selected from the group consisting of interferon beta-1a, and interferon beta-1b.

41. The ACC of any one of claims 1-40, wherein the CP1 and/or the CP2 comprises an IFab domain.

42. The ACC of claim 41, wherein the CP1 and/or the CP2 comprises an interleukin.

43. The ACC of claim 42, wherein the interleukin is selected from the group consisting of IL-1α, IL-1β, IL-1RA, IL-18, IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-3, IL-5, IL-6, IL-11, IL-12, IL-10, IL-20, IL-14, IL-16, and IL-17.

44. The ACC of any one or combination of claims 1-43, wherein the CM1 and/or the CM2 comprise a total of about 3 amino acids to about 15 amino acids.

45. The ACC of any one or combination of claims 1-44, wherein the CM1 and the CM2 comprise substrates for different proteases.

46. The ACC of any one or combination of claims 1-44, wherein the CM1 and the CM2 comprise substrates for the same protease.

47. The ACC of any one or combination of claims 1-46, wherein the protease(s) is/are selected from the group consisting of: ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17/TACE, ADAMDEC1, ADAMTS1, ADAMTS4, ADAMTS5, BACE, Renin, Cathepsin D, Cathepsin E, Caspase 1, Caspase 2, Caspase 3, Caspase 4, Caspase 5, Caspase 6, Caspase 7, Caspase 8, Caspase 9, Caspase 10, Caspase 14, Cathepsin B, Cathepsin C, Cathepsin K, Cathespin L, Cathepsin S, Cathepsin V/L2, Cathepsin X/Z/P, Cruzipain, Legumain, Otubain-2, KLK4, KLK5, KLK6, KLK7, KLK8, KLK10, KLK11, KLK13, KLK14, Meprin,

Neprilysin, PSMA, BMP-1, MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-19, MMP-20, MMP-23, MMP-24, MMP-26, MMP-27, activated protein C, cathepsin A, cathepsin G, Chymase, FVIIa, FIXa, FXa, FXIa, FXIIa, Elastase, Granzyme B, Guanidinobenzoatase, HtrA1, human neutrophil lyase, lactoferrin, marapsin, NS3/4A, PACE4, Plasmin, PSA, tPA, thrombin, tryptase, uPA, DESC1, DPP-4, FAP, Hepsin, Matriptase-2, MT-SP1/Matripase, TMPRSS2, TMPRSS3, and TMPRSS4.

48. The ACC of claim 47, wherein the protease(s) is/are selected from the group consisting of: uPA, legumain, MT-SP1, ADAM17, BMP-1, TMPRSS3, TMPRSS4, MMP-2, MMP-9, MMP-12, MMP-13, and MMP-14.

49. The ACC of claim 47, wherein the CM1 and/or the CM2 comprise a sequence selected from the group consisting of: LSGRSDNH (SEQ ID NO: 5), TGRGPSWV (SEQ ID NO: 6), PLTGRSGG (SEQ ID NO: 7), TARGPSFK (SEQ ID NO: 8), NTLSGRSENHSG (SEQ ID NO: 9), NTLSGRSGNHGS (SEQ ID NO: 10), TSTSGRSANPRG (SEQ ID NO: 11), TSGRSANP (SEQ ID NO: 12), VHMPLGFLGP (SEQ ID NO: 13), AVGLLAPP (SEQ ID NO: 14), AQNLLGMV (SEQ ID NO: 15), QNQALRMA (SEQ ID NO: 16), LAAPLGLL (SEQ ID NO: 17), STFPFGMF (SEQ ID NO: 18), ISSGLLSS (SEQ ID NO: 19), PAGLWLDP (SEQ ID NO: 20), VAGRSMRP (SEQ ID NO: 21), VVPEGRRS (SEQ ID NO: 22), ILPRSPAF (SEQ ID NO: 23), MVLGRSLL (SEQ ID NO: 24), QGRAITFI (SEQ ID NO: 25), SPRSIMLA (SEQ ID NO: 26), SMLRSMPL (SEQ ID NO: 27), ISSGLLSGRSDNH (SEQ ID NO: 28), AVGLLAPPGGLSGRSDNH (SEQ ID NO: 29), ISSGLLSSGGSGGSLSGRSDNH (SEQ ID NO: 30), LSGRSGNH (SEQ ID NO: 31), SGRSANPRG (SEQ ID NO: 32), LSGRSDDH (SEQ ID NO: 33), LSGRSDIH (SEQ ID NO: 34), LSGRSDQH (SEQ ID NO: 35), LSGRSDTH (SEQ ID NO: 36), LSGRSDYH (SEQ ID NO: 37), LSGRSDNP (SEQ ID NO: 38), LSGRSANP (SEQ ID NO: 39), LSGRSANI (SEQ ID NO: 40), LSGRSDNI

~~(SEQ ID NO: 41), MIAPVAYR (SEQ ID NO: 42), RPSPMWAY (SEQ ID NO: 43), WATPRPMR (SEQ ID NO: 44), FRLLDWQW (SEQ ID NO: 45), ISSGL (SEQ ID NO: 46), ISSGLLS (SEQ ID NO: 47), ISSGLL (SEQ ID NO: 48), ISSGLLSGRSANPRG (SEQ ID NO: 49), AVGLLAPPTSGRSANPRG (SEQ ID NO: 50), AVGLLAPPSGRSANPRG (SEQ ID NO: 51), ISSGLLSGRSDDH (SEQ ID NO: 52), ISSGLLSGRSDIH (SEQ ID NO: 53), ISSGLLSGRSDQH (SEQ ID NO: 54), ISSGLLSGRSDTH (SEQ ID NO: 55), ISSGLLSGRSDYH (SEQ ID NO: 56), ISSGLLSGRSDNP (SEQ ID NO: 57), ISSGLLSGRSANP (SEQ ID NO: 58), ISSGLLSGRSANI (SEQ ID NO: 59), AVGLLAPPGGLSGRSDDH (SEQ ID NO: 60), AVGLLAPPGGLSGRSDIH (SEQ ID NO: 61), AVGLLAPPGGLSGRSDQH (SEQ ID NO: 62), AVGLLAPPGGLSGRSDTH (SEQ ID NO: 63), AVGLLAPPGGLSGRSDYH (SEQ ID NO: 64), AVGLLAPPGGLSGRSDNP (SEQ ID NO: 65), AVGLLAPPGGLSGRSANP (SEQ ID NO: 66), AVGLLAPPGGLSGRSANI (SEQ ID NO: 67), ISSGLLSGRSDNI (SEQ ID NO: 68), AVGLLAPPGGLSGRSDNI (SEQ ID NO: 69), GLSGRSDNHGGAVGLLAPP (SEQ ID NO: 70), GLSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 71), LSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 72), ISSGLSS (SEQ ID NO: 73), PVGYTSSL (SEQ ID NO: 74), DWLYWPGI (SEQ ID NO: 75), LKAAPRWA (SEQ ID NO: 76), GPSHLVLT (SEQ ID NO: 77), LPGGLSPW (SEQ ID NO: 78), MGLFSEAG (SEQ ID NO: 79), SPLPLRVP (SEQ ID NO: 80), RMHLRSLG (SEQ ID NO: 81), LLAPSHRA (SEQ ID NO: 82), GPRSFGL (SEQ ID NO: 83), GPRSFG (SEQ ID NO: 84), SARGPSRW (SEQ ID NO: 85), GGWHTGRN (SEQ ID NO: 86), HTGRSGAL (SEQ ID NO: 87), AARGPAIH (SEQ ID NO: 88), RGPAFNPM (SEQ ID NO: 89), SSRGPAYL (SEQ ID NO: 90), RGPATPIM (SEQ ID NO: 91), RGPA (SEQ ID NO: 92), GGQPSGMWGW (SEQ ID NO: 93), FPRPLGITGL (SEQ ID NO: 94), SPLTGRSG (SEQ ID NO: 95), SAGFSLPA (SEQ ID NO: 96), LAPLGLQRR (SEQ ID NO: 97), SGGPLGVR (SEQ ID NO: 98), PLGL (SEQ ID NO: 99), and SGRSDNI (SEQ ID NO: 100).~~

50. The ACC of claim 47, wherein the CM1 and/or the CM2 comprises a sequence selected from the group consisting of: ISSGLLSGRSDNH (SEQ ID NO: 28), LSGRSDDH (SEQ ID NO: 33), ISSGLLSGRSDQH (SEQ ID NO: 54), SGRSDNI (SEQ ID NO: 100), and ISSGLLSGRSDNI (SEQ ID NO: 68).

51. The ACC of any one or combination of claims 1-50, wherein the CM1 and/or the CM2 comprises a sequence selected from SEQ ID Nos: 5-100 and 263-308.

52. The ACC of any one or combination of claims 1-51, wherein the protease(s) is/are produced by a tumor in a subject.

53. The ACC of claim 52, wherein the subject has been diagnosed or identified as having a cancer.

54. The ACC of any one or combination of claims 1-53, wherein the CP1 and the CM1 directly abut each other in the first monomer construct.

55. The ACC of any one or combination of claims 1-54, wherein the CM1 and the DD1 directly abut each other in the first monomer construct.

56. The ACC of any one or combination of claims 1-55, wherein the CP2 and the CM2 directly abut each other in the second monomer construct.

57. The ACC of any one or combination of claims 1-56, wherein the CM2 and the DD2 directly abut each other in the second monomer construct.

58. The ACC of any one or combination of claims 1-57, wherein the first monomer construct comprises at least one linker.

59. The ACC of claim 58, wherein the at least one linker is a linker L1 disposed between the CP1 and the CM1 and/or a linker L2 disposed between the CM1 and the DD1.

60. The ACC of claim 59, wherein the second monomer construct comprises at least one linker.

61. The ACC of claim 60, wherein the at least one linker is a linker L3 disposed between the CP2 and the CM2 and/or a linker L4 disposed between the CM2 and the DD2.

62. The ACC of claim 61, wherein the first monomer construct comprises a linker L1 and the second monomer construct comprises a linker L3.

63. The ACC of claim 62, wherein L1 and L3 are the same.

64. The ACC of claim 63, wherein the second monomer construct comprises a linker L2 and the second monomer construct comprises a linker L4.

65. The ACC of claim 64, wherein L2 and L4 are the same.

66. The ACC of claim 65, wherein each linker has a total length of 1 amino acid to about 15 amino acids.

67. The ACC of claim 66, wherein each linker has a total length of at least 5 amino acids.

68. The ACC of any one or combination of claims 1-67, wherein the first monomer construct comprises at least one linker, wherein each linker is independently selected from from the group consisting of GSSGGSGGSGG (SEQ ID NO: 210); GGGS (SEQ ID NO: 2); GGGSGGGS (SEQ ID NO: 211); GGGSGGGSGGGS

(SEQ ID NO: 212); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214); GGGGSGGGGS (SEQ ID NO: 215); GGGGS (SEQ ID NO: 216); GS; GGGGSGS (SEQ ID NO: 217); GGGGSGGGGSGGGGSGS (SEQ ID NO: 218); GGSLDPKGGGGS (SEQ ID NO: 219); PKSCDKTHTCPPCPAPELLG (SEQ ID NO: 220); SKYGPPCPPCPAPEFLG (SEQ ID NO: 221); GKSSGSGSESKS (SEQ ID NO: 222); GSTSGSGKSSEGKG (SEQ ID NO: 223); GSTSGSGKSSEGSGSTKG (SEQ ID NO: 224); GSTSGSGKPGSGEGSTKG (SEQ ID NO: 225); GSTSGSGKPGSSEGST (SEQ ID NO: 226); (GS)n, (GGS)n, (GSGGS)n (SEQ ID NO: 227), (GGGS)n (SEQ ID NO: 228), (GGGGS)n (SEQ ID NO: 216), wherein each n is an integer of at least one; GGSG (SEQ ID NO: 229); GGSGG (SEQ ID NO: 230); GSGSG (SEQ ID NO: 231; GSGGG (SEQ ID NO: 232); GGGSG (SEQ ID NO: 233); GSSSG (SEQ ID NO: 234); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214); and GSTSGSGKPGSSEGST (SEQ ID NO: 226).

69. The ACC of claim 68, wherein the linker comprises a sequence of GGGS (SEQ ID NO: 2).

70. The ACC of any one or combination of claims 1-69, wherein the first monomer construct, comprises in a N- to C- terminal direction, the CP1, the CM1, and, linked directly or indirectly to the C-terminus of the CM1, the DD1.

71. The ACC of any one or combination of claims 1-70, wherein the first polypeptide comprises in a C- to N-terminal direction, the CP1, the CM1, and, linked directly or indirectly to the N-terminus of the CM1, the DD1.

72. The ACC of any one or combination of claims 1-71, wherein the second polypeptide comprises in a N- to C-terminal direction, the CP2, CM2, and, linked directly or indirectly to the C-terminus of the CM2, the DD2.

73. The ACC of any one or combination of claims 1-72, wherein the second polypeptide comprises in a C- to N-terminal direction, the CP2, CM2, and, linked directly or indirectly to the CM2, the DD2.

74. The ACC of claim 70, wherein the first monomer construct comprises, in the N- to C-terminal direction, the CP1, the CM1, and the DD1, wherein the CP1 and the CM1 directly abut each other, wherein the CM1 and the DD1 directly abut each other, wherein the CM1 is a peptide of not more than 10 amino acids, wherein the second monomer construct is the same as the first monomer construct, and wherein the first and second monomer constructs are covalently bound to each other via at least two disulfide bonds.

75. The ACC of claim 74, wherein CP1 is an interferon.

76. The ACC of claim 75, wherein CP1 is an interferon-alpha.

77. The ACC of any one or combination of claims 1-76, wherein the at least one CP1 and/or CP2 activity is a binding affinity (K_D) of the CP1 and/or the CP2 for its cognate receptor as determined using surface plasmon resonance.

78. The ACC of any one or combination of claims 1-76, wherein the at least one CP1 and/or CP2 activity is a level of proliferation of lymphoma cells.

79. The ACC of any one or combination of claims 1-6, wherein the at least one CP1and/or CP2 activity is a level of JAK/STAT/ISGF3 pathway activation in a lymphoma cell.

80. The ACC of any one or combination of claims 1-76, wherein the at least one activity is a level of SEAP production in a lymphoma cell.

81. The ACC of any one or combination claims 1-80, wherein the ACC is characterized by at least a 20-fold reduction in at least one CP1 and/or CP2 activity as compared to the control level.

82. The ACC of claim 81, wherein the ACC is characterized by at least a 50-fold reduction in at least one CP1 and/or CP2 activity as compared to the control level.

83. The ACC of claim 82, wherein the ACC is characterized by at least a 100-fold reduction in at least one activity of the CP1 and/or CP2 as compared to the control level.

84. The ACC of claim 83, wherein the ACC is characterized by at least a 500-fold reduction in at least one CP1 and/or CP2 activity as compared to the control level.

85. The ACC of any one or combination of claims 1-84, wherein the control level of the at least one activity of the CP1 and/or CP2, is the activity of the CP1 and/or CP2 in the ACC following exposure of the ACC to the protease(s).

86. The ACC of any one or combination of claims 1-84, wherein the control level of the at least one CP1 and/or CP2, is the corresponding CP1 and/or CP2 activity of a corresponding wildtype mature cytokine.

87. The ACC of any one or combination of claims 1-86, wherein the ACC is characterized by generating a cleavage product following exposure to the protease(s), wherein the cleavage product comprises the at least one activity of the CP1 and/or CP2.

88. The ACC of claim 87, wherein the at least one activity of the CP1 and/or CP2 is anti-proliferation activity.

89. The ACC of claim 88, wherein the control level is an EC50 value, and wherein ratio of EC50 (cleavage product) to EC50 (control level) is less than about 10, or less than about 9, or less than about 8, or less than about 7, or less than about 6, or less than about 5, or less than about 4, or less than about 3, or less than about 2, or less than about 1.5.

90. A composition comprising an ACC of any one or combination of claims 1-89.

91. The composition of claim 90, wherein the composition is a pharmaceutical composition.

92. A container, vial, syringe, injector pen, or kit comprising at least one dose of the composition of claim 90 or 91.

93. A method of treating a subject in need thereof comprising administering to the subject a therapeutically effective amount of the ACC of any one or combination of claims 1-89 or the composition of claims 90 or 91.

94. The method of claim 93, wherein the subject has been identified or diagnosed as having a cancer.

95. The method of claim 94, wherein the cancer is a lymphoma, solid tumor, hematological tumor, sarcoma, osteosarcoma, glioblastoma, neuroblastoma, melanoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, B-cell neoplasms, multiple myeloma, B-cell lymphoma, B-cell non-Hodgkin's lymphoma, Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), myelodysplastic syndromes (MDS), cutaneous T-cell lymphoma, retinoblastoma, bladder cancer, stomach cancer, urothelial carcinoma, lung cancer, colon cancer, renal cell carcinoma, gastric and esophageal cancer, pancreatic cancer, prostate cancer, breast cancer, colorectal cancer, ovarian

~~cancer, non-small cell lung carcinoma, squamous cell head and neck carcinoma, endometrial cancer, cervical cancer, liver cancer, or hepatocellular carcinoma.~~

~~96. The method of claim 95, wherein the lymphoma is Burkitt's lymphoma.~~

~~97. A nucleic acid encoding a polypeptide that comprises the CP1 and CM1 of the ACC of any one or combination of claims 1-89.~~

~~98. The nucleic acid of claim 97, wherein the polypeptide further comprises a DD1 of any one or combination of claims 1-16 or claims 23-88.~~

~~99. A nucleic acid encoding a polypeptide that comprises the CP2 and CM2 of the ACC of any one or combination of claims 1-89.~~

~~100. The nucleic acid of claim 99, wherein the polypeptide further comprises the DD2 of any one or combination of claims 1-16 or claims 23-88.~~

~~101. A vector comprising the nucleic acid of any one or combination of claims 97-100.~~

~~102. The vector of claim 101, wherein the vector is an expression vector.~~

~~103. A cell comprising the nucleic acid of any one or combination of claims 96-99 or the vector of claim 101 or 102.~~

~~104. A pair of nucleic acids that together encode a polypeptide that comprises the CP1 and CM1 of the first monomer construct and a polypeptide that comprises the CP2 and CM2 of the second monomer construct of any one or combination of claims 1-89.~~

~~105. A pair of vectors that together comprise the pair of nucleic acids of claim 104.~~

106. The pair of vectors of claim 105, wherein the pair of vectors is a pair of expression vectors.

107. A cell comprising the pair of nucleic acids of claim 102 or the pair of vectors of claims 105 or 106.

108. A method of producing an ACC comprising:

culturing a cell of claim 103 or 107 in a liquid culture medium under conditions sufficient to produce the ACC; and

recovering the ACC from the cell or the liquid culture medium.

109. The method of claim 108, further comprising:

isolating the ACC recovered from the cell or the liquid culture medium.

110. The method of claim 109, further comprising:

formulating isolated ACC into a pharmaceutical composition.

111. An ACC produced by the method of claim 108.

112. A composition comprising an ACC of claim 111.

113. The composition of claim 112, wherein the composition is a pharmaceutical composition.

114. A container, vial, syringe, injector pen, or kit comprising at least one dose of the composition of claim 112 or 113.

115. An activatable cytokine construct (ACC) comprising a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1);

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2);

(c) the first monomer construct is a polypeptide comprising, in an N- to C-terminal direction, the CP1, the CM1, and the DD1, further wherein:

(i) each of the first monomer construct and the second monomer construct comprises a Linking Region comprising no more than 18 amino acids; and

(ii) the CP1 is a mature interferon;

(d) further wherein:

(i) the second monomer construct is the same as the first monomer construct,

(ii) the first and second monomer constructs are covalently bound to each other via at least one disulfide bond, and

(iii) the DD1 and the DD2 are a pair of human IgG Fc domains;

(e) the DD1 and the DD2 bind each other thereby forming a dimer of the first monomer construct and the second monomer construct; and

(f) the ACC is characterized by having a reduced level of interferon activity as compared to a corresponding control interferon.

116. The ACC of claim 115, wherein the CP1 is a mature human interferon alpha.

117. The ACC of any one or combination of claims 115-116, wherein the mature interferon is mature interferon alpha-2b.

118. The ACC of any one or combination of claims 115-117, wherein the mature interferon is a truncated form of a wild type mature interferon alpha-2b.

119. The ACC of any one or combination of claims 115-117, wherein the mature interferon comprises a sequence that is at least 95% identical to SEQ ID NO: 1.

120. The ACC of any one or combination of claims 115-117, wherein the mature interferon alpha comprises the sequence of SEQ ID NO: 1.

~~121. The ACC of any one or combination of claims 115-120, wherein the CP1 and the CM1 directly abut each other, the CM1 and the DD1 directly abut each other, and the CM1 and the CM2 each comprises no more than 10 amino acids, optionally no more than 7 amino acids.~~

~~122. The ACC of any one or combination of claims 115-121, wherein the CM1 and the CM2 each independently functions as a substrate of urokinase (uPa) and/or a matrix metalloproteinase (MMP).~~

~~123. The ACC of any one or combination of claims 115-122, wherein the CM1 and the CM2 each independently functions as a substrate of urokinase (uPa) and/or MMP-14.~~

~~124. The ACC of any one or combination of claims 115-123, wherein the CM1 and the CM2 each comprises a sequence that is at least 85% identical to SEQ ID NO: 100.~~

~~125. The ACC of any one or combination of claims 115-124, wherein the CM1 and the CM2 each comprises a sequence selected from the group consisting of SEQ ID NO: 41, SEQ ID NO: 68, and SEQ ID NO: 100.~~

~~126. The ACC of any one or combination of claims 115-125, wherein the DD1 and the DD2 are a pair of human IgG1 Fc domains or a pair of human IgG4 Fc domains.~~

~~127. The ACC of claim 126, wherein the DD1 and the DD2 are a pair of human IgG1 Fc domains truncated at N-terminus to Cysteine 226 as numbered by EU numbering or a pair of human IgG4 Fc domains truncated at N-terminus to Cysteine 226 as numbered by EU numbering.~~

~~128. The ACC of claim 126 or 127, wherein the DD1 and the DD2 are a pair of human IgG4 Fc domains that comprise a S228P mutation as numbered by EU numbering.~~

129. The ACC of any one or combination of claims 115-128, wherein the DD1 and the DD2 each comprises a sequence that is at least 95% identical to SEQ ID NO: 3.

130. The ACC of any one or combination of claims 115-129, wherein the DD1 and the DD2 each comprises a sequence of SEQ ID NO: 3.

131. The ACC of any one or combination of claims 115-130, wherein the first and second monomer constructs are covalently bound to each other via at least two disulfide bonds.

132. The ACC of any one or combination of claims 115-131, wherein the first and second monomer constructs are covalently bound to each other via at least three disulfide bonds.

133. The ACC of any one or combination of claims 115-132, wherein the first and second monomer constructs are covalently bound to each other via at least four disulfide bonds.

134. The ACC of any one or combination of claims 115-133, wherein the first monomer construct further comprises a signal sequence directly abutting the N-terminus of the CM1.

135. The ACC of claim 134, wherein the signal sequence comprises a sequence that is at least 95% identical to SEQ ID NO: 345.

136. The ACC of claim 134, wherein the signal sequence comprises the sequence of SEQ ID NO: 345.

137. The ACC of any one or combination of claims 115-136 wherein each of the first monomer construct and the second monomer construct comprises a Linking Region comprising no more than 12 amino acids.

138. The ACC of claim 137, wherein the Linking Region comprises 7 to 12 amino acids.

139. The ACC of claim 137, wherein the Linking Region comprises 7 amino acids.

140. The ACC of any one or combination of claims 115-139, wherein the ACC is characterized by at least a 500-fold reduction in interferon activity as compared to a corresponding control interferon.

141. The ACC of any one or combination of claims 115-140, wherein the CP1 is an interferon alpha and the control interferon is a recombinant interferon alpha.

142. The ACC of any one or combination of claims 115-140, wherein the CP1 is an interferon alpha-2b and the control interferon is pegylated interferon alpha-2b.

143. The ACC of any one or combination of claims 115-142, wherein the interferon activity is an anti-proliferation activity in lymphoma cells.

144. The ACC of any one or combination of claims 115-142, wherein the interferon activity is induction of secreted embryonic alkaline phosphatase production in interferon-responsive HEK293 cells.

145. The ACC of any of claims 115-144, wherein the ACC is further characterized by generating a cleavage product following exposure to the protease for which CM1 functions as a substrate, wherein the ratio of the interferon activity of the control

interferon to the cleavage product is less than about 2, and wherin the control interferon is a corresponding recombinant wildtype interferon or a corresponding pegylated interferon.

146. The ACC of claim 145, wherein the EC50 of the cleavage product is approximately the same as the EC50 of the corresponding recombinant wildtype interferon.

147. The ACC of claim 115, wherein the first and second monomer constructs each comprises a sequence that is at least 95% identical to SEQ ID NO: 313.

148. The ACC of claim 147, wherein the ACC is characterized by at least a 500-fold reduction in interferon activity as compared to wild type interferon alpha-2b, and wherein the ACC is further characterized by generating a cleavage product following exposure to uPA, wherein the cleavage product has approximately the same interferon activity as wildtype interferon alpha-2b, wherein interferon activity is measured in an anti-proliferation assay in lymphoma cells or in an assay of induction of secreted embryonic alkaline phosphatase production in interferon-responsive HEK293 cells.

149. The ACC of claim 147, wherein the ACC exhibits lower toxicity in vivo compared to either wildtype interferon alpha-2b or PEGylated interferon alpha-2b.

150. An activatable cytokine construct (ACC) comprising a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1);

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2);

(c) the first monomer construct is a polypeptide comprising, in an N- to C-terminal direction, the CP1, the CM1, and the DD1, further wherein:

(i) the CP1 and the CM1 directly abut each other,

(ii) the CM1 and the DD1 directly abut each other,

(iii) the CP1 comprises a sequence that is at least 85% identical to SEQ ID NO: 1,

(iv) the CM1 comprises a sequence that is at least 85% identical to SEQ ID: 100,

(d) further wherein:

(i) the second monomer construct is the same as the first monomer construct,

(ii) the first and second monomer constructs are covalently bound to each other via at least one disulfide bond, and

(iii) the DD1 and DD2 are a pair of human IgG4 Fc domains;

(e) the DD1 and the DD2 bind each other thereby forming a dimer of the first monomer construct and the second monomer construct; and

(f) the ACC is characterized by having a reduced level of interferon alpha activity as compared to the interferon alpha activity of PEGylated interferon alpha-2b.

151. A composition comprising the ACC of any one or combination of claims 115-150.

152. The composition of claim 151, where the composition is a pharmaceutical composition.

153. A container, vial, syringe, injector pen, or kit comprising at least one dose of the composition of claim 151 or 152.

154. A method of treating a subject in need thereof comprising administering to the subject a therapeutically effective amount of the ACC of any one or combination of claims 115-150 or the composition of claim 151 or 152.

155. The method of claim 154, wherein the subject has been identified or diagnosed as having a cancer.

156. A nucleic acid encoding a polypeptide that comprises the first monomer of the ACC of any one or combination of claims 115-150.

157. A vector comprising the nucleic acid of claim 156.

158. The vector of claim 157, wherein the vector is an expression vector.

159. A mammalian cell comprising the nucleic acid of claim 156 or the vector of claim 157 or 158.

160. The mammalian cell of claim 159, wherein the mammalian cell is an HEK293 cell or a CHO cell.

161. A method of manufacturing an ACC, the method comprising:

a. expressing the ACC in the mammalian cell of claim 159 or 160; and

b. purifying the expressed ACC.

162. The ACC of any one or combination of claims 115-150, wherein the CM1 functions as a substrate for a protease that is over-expressed in a tumor tissue.

CLAIMS

1. An activatable cytokine construct (ACC) comprising a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1);

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2);

(c) the first monomer construct is a polypeptide comprising, in an N- to C-terminal direction, the CP1, the CM1, and the DD1 and the first monomer construct is characterized in that the CP1 and the DD1 are linked by a Linking Region of no more than 18 amino acids such that the Linking Region of no more than 18 amino acids includes the CM1, further wherein:

the CP1 is a mature interferon;

(d) further wherein:

(i) the second monomer construct is the same as the first monomer construct, and

(ii) the DD1 and the DD2 are a pair of human IgG Fc domains;

(e) the DD1 and the DD2 are covalently bound to each other via at least one disulfide bond thereby forming a dimer of the first monomer construct and the second monomer construct; and

(f) the ACC is characterized by having a reduced level of interferon activity as compared to a corresponding control interferon.

2. The ACC of claim 1, wherein the CP1 is a mature human interferon alpha.

3. The ACC of claim 2, wherein the mature interferon is mature interferon alpha-2b.

4. The ACC of claim 3, wherein the mature interferon comprises a sequence that is at least 95% identical to SEQ ID NO: 1.

5. The ACC of claim 3, wherein the mature interferon alpha comprises the sequence of SEQ ID NO: 1.

6. The ACC of claim 1, wherein the CM1 and the CM2 each comprises no more than 7 amino acids.

7. The ACC of claim 1, wherein each of the CM1 and the CM2 is independently cleavable by a urokinase (uPa) and/or a matrix metalloproteinase (MMP).

8. The ACC of claim 1, wherein the CM1 and the CM2 each comprises a sequence that is at least 85% identical to SEQ ID NO: 100.

9. The ACC of claim 1, wherein the CM1 and the CM2 each comprises a sequence selected from the group consisting of SEQ ID NO: 41, SEQ ID NO: 68, and SEQ ID NO: 100.

10. The ACC of claim 1, wherein the DD1 and the DD2 are a pair of human IgG4 Fc domains.

11. The ACC of claim 1, wherein the DD1 and the DD2 are a pair of human IgG1 or IgG4 Fc domains truncated at the N-terminus to Cysteine 226 as numbered by EU numbering.

12. The ACC of claim 10, wherein the human IgG4 Fc domains comprise a S228P mutation as numbered by EU numbering.

13. The ACC of claim 1, wherein the DD1 and the DD2 each comprises a sequence that is at least 95% identical to SEQ ID NO: 3.

14. The ACC of claim 1, wherein the DD1 and the DD2 each comprises the sequence of SEQ ID NO: 3.

15. The ACC of claim 1, wherein the first and second monomer constructs are covalently bound to each other via at least two disulfide bonds.

16. The ACC of claim 1, wherein the first and second monomer constructs are covalently bound to each other via at least three disulfide bonds.

17. The ACC of claim 1, wherein the first and second monomer constructs are covalently bound to each other via at least four disulfide bonds.

18. The ACC of claim 1, wherein each of the first and second monomer constructs comprises a sequence that is at least 95% identical to SEQ ID NO: 313.

19. An activatable cytokine construct (ACC) comprising a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1);

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2);

(c) the first monomer construct is a polypeptide comprising, in an N- to C-terminal direction, the CP1, the CM1, and the DD1, further wherein:

(i) each of the first monomer construct and the second monomer construct comprises a Linking Region comprising no more than 18 amino acids, and

(ii) the CP1 is a mature interferon;

(d) further wherein:

(i) the second monomer construct is the same as the first monomer construct, and

(ii) the DD1 and the DD2 are a pair of human IgG Fc domains;

(e) the DD1 and the DD2 are covalently bound to each other via at least one disulfide bond thereby forming a dimer of the first monomer construct and the second monomer construct; and

(f) the ACC is characterized by having a reduced level of interferon activity as compared to a corresponding control interferon, wherein each of the first and second monomer constructs comprises SEQ ID NO: 313.

20. An activatable cytokine construct (ACC) comprising a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1) in an N- to C-terminal direction, wherein the CP1 and the CM1 directly abut each other and the CM1 and the DD1 directly abut each other;

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2) in an N- to C-

terminal direction, wherein the CP2 and the CM2 directly abut each other and the CM2 and the DD2 directly abut each other;

(c)

wherein the CP1 is a mature interferon and

the CM1 comprises a sequence that is at least 85% identical to SEQ ID: 100,

(d) further wherein:

(i) the second monomer construct is the same as the first monomer construct, and

(ii) the DD1 and DD2 are a pair of human IgG1 or IgG4 Fc domains;

(e) the DD1 and the DD2 are covalently bound to each other via at least one disulfide bond thereby forming a dimer of the first monomer construct and the second monomer construct; and

(f) the ACC is characterized by having a reduced level of interferon alpha activity as compared to the interferon alpha activity of PEGylated interferon alpha-2b.

21. An activatable cytokine construct (ACC) that includes a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1),

wherein the CM1 is positioned between the CP1 and the DD1 and the first monomer construct is characterized in that the CP1 and the DD1 are linked by a Linking Region of no more than 18 amino acids such that the Linking Region of no more than 18 amino acids includes the CM1; and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2), wherein the CM2 is positioned between the CP2 and the DD2 and the second monomer construct is characterized in that the CP2 and the DD2 are linked by a Linking Region of no more than 18 amino acids such that the Linking Region of no more than 18 amino acids includes the CM2; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first dimerization domain (DD1), and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a cleavable moiety (CM), and a second dimerization domain (DD2), wherein the CM is positioned between the CP2 and the DD2, wherein the CM functions as a substrate for a protease and the second monomer construct is characterized in that the CP2 and the DD2 are linked by a Linking Region of no more than 18 amino acids such that the Linking Region of no more than 18 amino acids includes the CM2; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a cleavable moiety (CM), and a first dimerization domain (DD1), wherein the CM is positioned between the CP1 and the DD1 and the first monomer construct is characterized in that the CP1 and the DD1 are linked by a Linking Region of no more than 18 amino acids such that the Linking Region of no more than 18 amino acids includes the CM1, and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), and a second dimerization domain (DD2),

wherein the CM functions as a substrate for a protease; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), and a first dimerization domain (DD1), and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), and a second dimerization domain (DD2), wherein the CP1, the CP2, or both CP1 and CP2 include(s) an amino acid sequence that functions as a substrate for a protease and the first monomer construct is characterized in that the CP1 and the DD1 are linked by a Linking Region of no more than 18 amino acids and the second monomer construct is characterized in that the CP2 and the DD2 are linked by a Linking Region of no more than 18 amino acids;

wherein CP1 and CP2 are mature interfereons;

wherein the DD1 and the DD2 bind each other thereby forming a dimer of the first monomer construct and the second monomer construct;

wherein the ACC is characterized by having a reduced level of CP1 or CP2 activity as compared to a control level of the CP1 or CP2 activity, and

wherein the first monomer construct and the second monomer construct have a structure, wherein CP1 and CP2 are N-terminal to DD1 and DD2, respectively, in each construct.

22. The ACC of claim 21, wherein the DD1 and the DD2 are a pair of Fc domains.

23. The ACC of claim 22, wherein the pair of Fc domains is a pair of human Fc domains.

24. The ACC of claim 23, wherein the human Fc domains are human IgG1 Fc domains, human IgG2 Fc domains, human IgG3 Fc domains, or human IgG4 Fc domains.

25. The ACC of claim 24, wherein the human Fc domains are human IgG4 Fc domains.

26. The ACC of claim 23, wherein the human Fc domains comprise a sequence that is at least 90% identical to SEQ ID NO: 3, SEQ ID NO: 315, or SEQ ID NO: 316.

27. The ACC of claim 23, wherein the human Fc domains comprise SEQ ID NO: 3, SEQ ID NO: 315, or SEQ ID NO: 316.

28. The ACC of claim 21, wherein the CP1 and/or CP2 comprises a sequence that is at least 95% identical to SEQ ID NO: 1.

29. The ACC of claim 21, wherein the CP1 and/or CP2 comprises a sequence of SEQ ID NO: 1.