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 peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1), wherein the CM1 is positioned between the CP1 and the DD1 and the CM3 is positioned between the PM1 and the CP1; 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;

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

the ACC is characterized in that it has at least one of the following characteristics:

(i) a structural arrangement in an N- to C-terminal direction comprising: PM1-CM3-CP1-CM1-DD1 and CP2-CM2-DD2, wherein DD1 and DD2 are dimerized;

(ii) wherein 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 CM3;

(iii) wherein 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;

(iv) wherein each of PM1 and PM2 is less than 40 amino acids;

(v) wherein each of PM1 and PM2 is between 13 and 49 amino acids; and/or

(vi) wherein each of PM1 and PM2 is not a receptor for the CP1 and the CP2 and wherein each of PM1 and PM2 is not a fragment of receptor for the CP1 and the CP2.

2. The ACC of claim 1, wherein the second monomer construct further comprises a second peptide mask (PM2) and a fourth cleavable moiety (CM4), wherein the CM4 is positioned between the PM2 and the CP2; and/or wherein the first monomer construct

comprises a first polypeptide that comprises the PM1, the CM3, the CP1, the CM1, and the DD1; and/or wherein the second monomer construct comprises a second polypeptide that comprises the CP2, the CM2, and the DD2; and/or wherein the second monomer construct comprises a second polypeptide that comprises the PM2, the CM4, the CP2, the CM2, and the DD2.

3. The ACC of any one or combination of claims 1-2, 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, optionally wherein the CP1 and/or the CP2 is independently selected from IL-2, IL-7, IL-8, IL-10, IL-12, IL-15, IL-21, an IFN-alpha, an IFN beta, an IFN gamma, GM-CSF, TGF-beta, LIGHT, GITR-L, CD40L, CD27L, 4-1BB-L, OX40, and OX40L.

4. The ACC of any one or combination of claims 1-3, wherein:
the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 328, 329, 323, and 331-369, and the CP1 is an interferon;
the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 328, 329, 323, and 331-364, and the CP1 is an interferon alpha;
the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 331-360, 362-364, and the CP1 is an interferon beta;
the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 331-360, 366-369, and the CP1 is an interferon gamma;
the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 370-374, and the CP1 is an IL-12;
the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 375-382, 469-477, 478, and the CP1 is an IL-15;
the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 383-468, 469-478, and the CP1 is an IL-2; or

the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 478 and 479, and the CP1 is an IL-21.

5. The ACC of any one or combination of claims 2-4, wherein:
the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 328, 329, 323, and 331-369, and the CP2 is an interferon;
the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 328, 329, 323, and 331-364, and the CP2 is an interferon alpha;
the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 331-360, 362-364, and the CP2 is an interferon beta;
the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 331-360, 366-369, and the CP2 is an interferon gamma;
the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 370-374, and the CP2 is an IL-12;
the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 375-382, 469-477, 478, and the CP2 is an IL-15;
the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 383-468, 469-478, and the CP2 is an IL-2; or
the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 478 and 479, and the CP2 is an IL-21; and/or wherein PM1, PM2, or PM1 and PM2 comprises SEQ ID NO: 323, 331, or 332.

6. The ACC of any one or combination of claims 1 to 5, 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.

7. The ACC of claim 6, wherein the DD1 and the DD2 are a pair of Fc domains.

8. The ACC of any one or combination of claims 1-7, wherein the CP1 and the CP2 are the same.

9. The ACC of any one or combination of claims 1-7, wherein the CP1 and/or the CP2 is/are an interferon; or optionally, wherein the CP1 and the CP2 are an interferon; or optionally, wherein the CP1 and/or the CP2 comprises an interleukin.

10. The ACC of any one or combination of claims 1-9, wherein the first monomer construct comprises at least one linker; or optionally, wherein the at least one linker is a linker L1 disposed between the PM1 and the CM3 and/or a linker L2 disposed between the CM3 and the CP1; or optionally, wherein the second monomer construct comprises at least one linker, optionally wherein the at least one linker is a linker L3 disposed between the PM2 and the CM4 and/or a linker L4 disposed between the CM4 and the CP2; or optionally, wherein the first monomer construct comprises a linker L1 and the second monomer construct comprises a linker L3; or optionally, wherein L1 and L3 are the same.

11. The ACC of claim 10, wherein the first monomer construct comprises a linker L2 and the second monomer construct comprises a linker L4; or optionally, wherein L2 and L4 are the same.

12. The ACC of any one or combination of claims 10-11, wherein each linker has a total length of 1 amino acid to about 15 amino acids; or optionally, wherein each linker has a total length of at least 5 amino acids.

13. The ACC of any one or combination of claims 1-12, wherein the first monomer construct comprises in a N- to C- terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1; or optionally, wherein the first polypeptide comprises in a C- to N-terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1.

14. The ACC of any one or combination of claims 1-13, wherein the second polypeptide comprises in a N- to C-terminal direction, the CP2, CM2, and the DD2.

15. The ACC of any one or combination of claims 1-13, wherein the second polypeptide comprises in a C- to N-terminal direction, the CP2, CM2, and the DD2.

16. The ACC of any one or combination of claims 1-13, wherein the first monomer construct comprises in a N- to C- terminal direction, the PM1, an optional linker, the CM3, an optional linker, 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.

17. The ACC of any one or combination of claims 1-16, wherein 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 at least one CP1 and/or CP2 activity.

18. The ACC of claim 17, wherein the at least one of the CP1 and the CP2 activity is a level of proliferation of lymphoma cells; or optionally, wherein the at least one of the CP1and the CP2 activity is the level of JAK/STAT/ISGF3 pathway activation in a lymphoma cell; or optionally, wherein the at least one activity is a level of SEAP production in a lymphoma cell; or optionally, wherein the ACC is characterized by at least a 2-fold reduction in at least one of the CP1 and the CP2 activity as compared to the control level; or optionally, wherein the ACC is characterized by at least a 5-fold reduction in at least one CP1 and/or the CP2 activity as compared to the control level; or optionally, wherein the ACC is characterized by at least a 10-fold reduction in at least one activity of the CP1 and/or the CP2 as compared to the control level; or optionally, wherein the ACC is characterized by at least a 500-fold reduction in at least one CP1 and/or the CP2 activity as compared to the control level.

19. The ACC of any one or combination of claims 17-18, wherein the control level of the at least one activity of the CP1 and/or the CP2, is the activity of the CP1 and/or the CP2 in the ACC following exposure of the ACC to the protease(s); or optionally, wherein the control level of the at least one CP1 and/or CP2, is the corresponding CP1 and/or the CP2 activity of a corresponding wildtype mature cytokine; or optionally, 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 the CP2; or optionally, wherein the at least one activity of the CP1 and/or the CP2 is anti-proliferation activity, and 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, or less than about 1.0.

20. The ACC of any one or combination of claims 1-19, wherein the first monomer construct is characterized in that the CP1 and the DD1 are linked by a linking region of no more than 12 amino acids such that the linking region of no more than 12 amino acids includes the CM3; or optionally, wherein the second monomer construct is characterized in that the CP2 and the DD2 are linked by a linking region of no more than 12 amino acids such that the linking region of no more than 12 amino acids includes the CM2; or optionally, wherein the PM1 comprises less than 50 amino acids; or optionally, wherein the PM2 comprises less than 50 amino acids; or optionally, wherein each of PM1 and PM2 is less than 19 amino acids; or optionally, wherein the PM1 is not a latency associated peptide and the PM2 is not a latency associated peptide; or optionally, wherein the PM1 is not a cytokine and the PM2 is not a cytokine; or optionally, wherein the PM1 is not a receptor for a cytokine and is not a fragment of a receptor for a cytokine; or optionally, wherein the PM2 is not a receptor for a cytokine and is not a fragment of a receptor for a cytokine; or optionally, wherein the PM1 is not an albumin and the PM2 is not an albumin.

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

(a) the first monomer construct is a polypeptide comprising a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1);

(b) the second monomer construct is a polypeptide comprising a second peptide mask (PM2), a second mature cytokine protein (CP2), a second and a fourth cleavable moieties (CM2 and CM4), and a second dimerization domain (DD2);

(c) the first monomer construct comprises, in an N- to C- terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1, further wherein:

(i) the PM1 comprises no more than 20 amino acids and binds to the CP1,

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

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

(iv) the CM1 comprises no more than 12 amino acids,

(v) the CM1 and the CM3 each functions as a substrate for a protease, and

(vi) the CP1 is a mature interferon;

(d) further wherein:

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

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

(iii) the DD1 and the DD2 bind to each other via at least one disulfide bond,

thereby forming a homodimer of the first monomer construct and the second monomer construct; and

(e) the ACC is characterized by having a reduced level of interferon activity as compared to a corresponding wildtype interferon or a corresponding pegylated interferon.

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

(a) the first monomer construct comprises a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1);

(b) the second monomer construct is a polypeptide comprising a second peptide mask (PM2), a second mature cytokine protein (CP2), a second and a fourth cleavable moieties (CM2 and CM4), and a second dimerization domain (DD2);

(c) the first monomer construct is a polypeptide comprising, in an N- to C- terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1, further wherein:

(i) the PM1 comprises a sequence that is at least 85% identical to SEQ ID NO: 323,

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

(iii) the CM1 comprises a sequence that is at least 85% identical to SEQ ID NO: 41, and

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

(d) further wherein:

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

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

(e) the DD1 and the DD2 covalently bind to each other via at least one disulfide bond, thereby forming a homodimer 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.

23. The ACC of any one or combination of claims 1-22 comprising a Linking Region comprising no more than 12 amino acids; or optionally, wherein the Linking Region comprises 7 to 12 amino acids; or optionally, wherein the Linking Region comprises 7 amino acids.

24. A composition comprising an ACC of any one or a combination of claims 1-23.

25. The composition of claim 24, wherein the composition is a pharmaceutical composition.

26. Use of the ACC of any one of claims 1-23 or the composition of claims 24 or 25 in the manufacture of a medicament for the treatment of a cancer.

27. A nucleic acid encoding a polypeptide that comprises the CP1 and the CM1 of the ACC of any one or a combination of claims 1-23; or optionally, wherein the polypeptide further comprises the DD1 of any one or combination of claims 1-23.

28. A nucleic acid encoding a polypeptide that comprises the CP2 and the CM2 of the ACC of any one or combination of claims 1-23; or optionally, wherein the polypeptide further comprises the DD2 of any one or combination of claims 1-23.

29. A vector comprising the nucleic acid of any one or a combination of claims 27-28; or optionally, wherein the vector is an expression vector.

30. A cell comprising the nucleic acid of any one or a combination of claims 27-28 or the vector of claim 29.

31. A method of producing an ACC comprising:
    a. culturing a cell of claim 30 in a liquid culture medium under conditions sufficient to produce the ACC; and
    b. recovering the ACC from the cell or the liquid culture medium.

32. The method of claim 31, further comprising: isolating the ACC recovered from the cell or the liquid culture medium; or optionally further comprising, formulating isolated ACC into a pharmaceutical composition.

33. The ACC of any one of claims 1-23 or the composition of claims 24 or 25, for use as a medicament.

34. The ACC of any one of claims 1-23 or the composition of claims 24 or 25, for use in the treatment of a cancer.