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 recombinant wildtype interferon or a corresponding pegylated 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 recombinant wildtype interferon or a corresponding pegylated 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 interferons;

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 level of activity of a recombinant wildtype interferon corresponding to the CP1 or the CP2, 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.