significant impact on the production process. Growth parameters are determined specifically for each cell line and these parameters are measured frequently to assure optimal growth and production conditions.

When the cells grow to sufficient numbers, they are transferred to large-scale production tanks and grown for a longer period of time. At this point in the process, the recombinant protein can be harvested. Typically, the cells are engineered to secrete the polypeptide into the cell culture media, so the first step in the purification process is to separate the cells from the media. Typically, harvesting includes centrifugation and filtration to produce a Harvested Cell Culture Fluid (HCCF). The media is then subjected to several additional purification steps that remove any cellular debris, unwanted proteins, salts, minerals or other undesirable elements. At the end of the purification process, the recombinant protein is highly pure and is suitable for human therapeutic use.

Although this process has been the subject of much study and improvements over the past several decades, the production of recombinant proteins is still not without difficulties. Thus, for example, during the recombinant production of polypeptides comprising disulfide bonds, especially multi-chain polypeptides comprising inter-chain disulfide bonds such as antibodies, it is essential to protect and retain the disulfide bonds throughout the manufacturing, recovery and purification process, in order to produce properly folded polypeptides with the requisite biological activity.

SUMMARY ~~OF THE INVENTION~~

The instant disclosure ~~invention~~ generally relates to a method for preventing reduction of a disulfide bond in a polypeptide expressed in a recombinant host cell, comprising supplementing the pre-harvest or harvested culture fluid of the recombinant host cell with an inhibitor of thioredoxin or a thioredoxin-like protein.

In one aspect, there is provided a method for the prevention of the reduction of a disulfide bond of an antibody expressed by a recombinant host cell, comprising
(A) following fermentation, supplementing the pre-harvest cell culture fluid (CFF) or harvested cell culture fluid (HCCF) comprising the antibody with a thioredoxin inhibitor selected from the group consisting of: (i) a direct inhibitor of thioredoxin; (ii) a specific inhibitor of thioredoxin reductase; (iii) a metal ion; (iv) an inhibitor of G6PD; (v) an inhibitor of hexokinase activity; and (vi) cystine, cysteine, or oxidized glutathione and/or
(B) air sparging the HCCF comprising the antibody.

In one aspect, there is provided a method for the prevention of the reduction of a disulfide bond of an antibody expressed by a recombinant eukaryotic host cell, comprising decreasing the level of an enzyme of the Trx system in the eukaryotic host cell, whereby the reduction of the disulfide bond of the antibody is prevented in the pre-harvest cell culture fluid (CFF) or harvested cell culture fluid (HCCF).

In one embodiment, the thioredoxin inhibitor is added to the pre-harvest culture fluid.

In another embodiment, the thioredoxin inhibitor is added to the harvested culture fluid.

In a further embodiment, the thioredoxin inhibitor is a direct inhibitor of thioredoxin.

In all embodiments, the thioredoxin inhibitor may, for example, be an alkyl-2-imidazolyl disulfide or a naphthoquinone spiroketal derivative.

In a further embodiment, the thioredoxin inhibitor is a specific inhibitor of thioredoxin reductase.

In a still further embodiment, the thioredoxin inhibitor is a gold complex, where the gold complex may, for example, be aurothioglucose (ATG) or aurothiomalate (ATM). While

the effective inhibitory concentration may vary, it typically is between about 0.1 mM and 1 mM. Similarly, the minimum effective inhibitory concentration varies depending on the nature of the polypeptide and overall circumstances, and is typically reached when the ATG or ATG concentration is at least about four-times of thioreduxin concentration in the pre-harvest or harvested culture fluid.

In another embodiment ~~of this aspect~~ of the disclosure ~~invention~~, the thioredoxin inhibitor is a metal ion, where the metal ion, without limitation, may be selected from the group consisting of Hg^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+}, and Mn^{2+}. When the metal ion is added in the form of cupric sulfate, the effective inhibitory concentration generally is between about 5 μM and about 100 μM, or between about 10 μM and about 80 μM, or between about 15 μM and about 50 μM. The minimum inhibitory concentration of cupric sulfate also varies, but typically is reached when cupric sulfate is added at a concentration at least about two-times of thioredoxin concentration in the pre-harves or harvested culture fluid.

In different embodiment, the thioredoxin inhibitor is an oxidizing agent, e.g., an inhibitor of G6PD, such as, for example, pyridoxal 5'-phosphate, 1 fluoro-2,4 dinitrobenzene, dehydroepiandrosterone (DHEA) or epiandrosterone (EA) ; cystine or cysteine. Typical effective inhibitor concentrations of DHEA are between ~~about~~ about 0.05 mM and about 5 mM, or between about 0.1 mM and about 2.5 mM.

In a further embodiment, the thioredoxin inhibitor is an inhibitor of hexokinase activity, including, without limitation, chelators of metal ions, such as, for example, ethylenediamine tetraacetic acid (EDTA). EDTA is typically added and effective at a concentration between about 5 mM and about 60 mM, or about 10 mM and about 50 mM, or about 20 mM and about 40 mM.

In other preferred embodiments, the inhibitor of hexokinase activity is selected from the group consisting of sorbose-1-phosphate, polyphosphates, 6-deoxy-6-fluoroglucose, 2-C-hydroxy-methylglucose, xylose, and lyxose.

Other inhibitors include cystine, cysteine, and oxidized glutathione which are typically added at a concentration at least about 40-times of the concentration of the polypeptide in question in the pre-harvest or harvested culture fluid.

In a still further embodiment, the thioredoxin inhibitor is an s iRNA, an antisense nucleotide, or an antibody specifically binding to a thioredoxin reductase.

In another embodiment, the thioredoxin inhibitor is a measure indirectly resulting in the inhibition of thioredoxin activity. This embodiment includes, for example, air sparging the

In yet another embodiment, the therapeutic antibody is an antibody that binds to VEGF. The anti-VEGF antibody may, for example, comprise a heavy and/or light chain variable domain sequence selected from the group consisting of SEQ ID NOS: 20 through 25.

In an additional embodiment, the therapeutic antibody is an antibody that binds CD11a. The anti-CD11a antibody may, for example, comprise a heavy and/or light chain variable domain sequence selected from the group consisting of SEQ ID NOS: 26 through 29.

In a further embodiment, the therapeutic antibody binds to a DR5 receptor. The anti-DR5 antibody may, for example, be selected from the group consisting of Apomabs 1.1, 2.1, 3.1, 4.1, 5.1, 5.2, 5.3 , 6.1, 6.2, 6.3, 7.1, 7.2, 7.3,8.1, 8.3, 9.1, 1.2, 2.2, 3.2, 4.2, 5.2, 6.2, 7.2, 8.2, 9.2, 1.3, 2.2, 3.3, 4.3, 5.3, 6.3, 7.3, 8.3, 9.3, and 25.3, and preferably is Apomab 8.3 or Apomab 7.3, and most preferably Apomab 7.3.

In other embodiments of the method of the present disclosure ~~invention~~, the polypeptide expressed in the recombinant host cell is a therapeutic polypeptide. For example, the therapeutic polypeptide can be selected from the group consisting of a growth hormone, including human growth hormone and bovine growth hormone; growth hormone releasing factor; parathyroid hormone; thyroid stimulating hormone; lipoproteins; alpha-1-antitrypsin; insulin A-chain; insulin B-chain; proinsulin; follicle stimulating hormone; calcitonin; luteinizing hormone; glucagon; clotting factors such as factor VIIIC, factor IX, tissue factor, and von Willebrands factor; anti-clotting factors such as Protein C; atrial natriuretic factor; lung surfactant; a plasminogen activator, such as urokinase or human urine or tissue-type plasminogen activator (t-PA); bombesin; thrombin; hemopoietic growth factor; tumor necrosis factor-alpha and -beta; enkephalinase; RANTES (regulated on activation normally T-cell expressed and secreted); human macrophage inflammatory protein (MIP-1-alpha); a serum albumin such as human serum albumin; Muellerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; a microbial protein, such as beta-lactamase; DNase; IgE; a cytotoxic T-lymphocyte associated antigen (CTLA), such as CTLA-4; inhibin; activin; vascular endothelial growth factor (VEGF); receptors for hormones or growth factors; Protein A or D; rheumatoid factors; a neurotrophic factor such as bone-derived neurotrophic factor (BDNF), neurotrophin-3, -4, -5, or -6 (NT-3, NT-4, NT-5, or NT-6), or a nerve growth factor such as NGF-β; platelet-derived growth factor (PDGF); fibroblast growth factor such as aFGF and bFGF; epidermal growth factor (EGF); transforming growth factor (TGF) such as TGF-alpha and TGF-beta, including TGF-β1, TGF-β2, TGF-β3, TGF-β4, or TGF-β5; insulin-like growth factor-I and -II (IGF-I and IGF-II); des(1-3)-IGF-I (brain IGF-I), insulin-like growth factor binding proteins; CD proteins such as CD3, CD4, CD8, CD19, CD20, CD34, and CD40;

WHAT IS CLAIMED:

1. A method for the prevention of the reduction of a disulfide bond of an antibody expressed by a recombinant host cell, comprising,

(A) following fermentation, supplementing the pre-harvest cell culture fluid (CFF) or harvested cell culture fluid (HCCF) comprising the antibody with a thioredoxin inhibitor selected from the group consisting of:

(i) a direct inhibitor of thioredoxin;

(ii) a specific inhibitor of thioredoxin reductase;

(iii) a metal ion;

(iv) an inhibitor of G6PD;

(v) an inhibitor of hexokinase activity; and

(vi) cystine, cysteine, or oxidized glutathione.

and/or

(B) air sparging the HCCF comprising the antibody.

2. The method of claim 1(i) wherein said thioredoxin inhibitor is an alkyl-2-imidazolyl disulfide or a naphthoquinone spiroketal derivative.

3. The method of claim 1(ii) wherein said thioredoxin inhibitor is a gold complex.

4. The method of claim 3 wherein said gold complex is aurothioglucose (ATG) or aurothiomalate (ATM), and, optionally, said ATG or said ATM is added at a concentration (a) between about 0.1 mM and about 1 mM, or (b) at least about four-times of thioredoxin reductase concentration in said pre-harvest or harvested culture fluid.

5. The method of claim 1 (iii) wherein said metal ion is selected from the group consisting of Hg^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+}, and Mn^{2+}.

6. The method of claim 5, wherein said metal ion is Cu^{2+} present in the form of cupric sulfate.

7. The method of claim 6 wherein said cupric sulfate is:

(a) in the form of pentrahydrate or in anhydrous form;

(b) added in a concentration between about 5 μM and about 100 μM;

(c) added in a concentration between about 10 μM to about 80 μM;

(d) added in a concentration between about 15 μM and about 50 μM; or

(e) added at a concentration at least about two-times of thioredoxin concentration in said pre-harvest or harvested culture fluid.

8. The method of claim 1(iv) wherein said thioredoxin inhibitor is selected from the group consisting of pyridoxal 5'-phosphate, 1 fluoro-2,4 dinitrobenzene, dehydroepiandrosterone (DHEA) and epiandrosterone (EA).

9. The method of claim 8 wherein said DHEA is added in a concentration (a) between about 0.05 mM and about 5 mM, or (b) between about 0.1 mM and about 2.5 mM.

10. The method of claim 1(v) wherein said thioredoxin inhibitor is:

(a) a chelator of metal ions; or

(b) selected from the group consisting of sorbose-1-phosphatc, polyphosphates, 6-deoxy-6-fluoroglucose, 2-C-hydroxy-methylglucose, xylose, and lyxose.

11. The method of claim 10(a) wherein said chelator of metal ions is ethylenediamine tetraacetic acid (EDTA).

12. The method of claim 11 wherein said EDTA is added in a concentration (i) between about 5 mM and about 60 mM; (ii) between about 10 mM and about 50 mM; or (iii) between about 20 mM and about 40 mM.

13. The method of claim 1(vi) wherein said cystine, cysteine or oxidized glutathione is added at a concentration at least about 40-times of the concentration of said antibody in said pre-harvest or harvested culture fluid.

14. The method of any one of the preceding claims wherein the antibody is a therapeutic antibody, a multispecific antibody or a biologically functional fragment thereof.

15. The method of claim 14 wherein (i) said antibody fragment is selected from the group consisting of Fab, Fab', F(ab')2, scFv, (scFv)2, dAb, complementarity determining region

(CDR) fragments, linear antibodies, single-chain antibody molecules, minibodies, diabodies, and a fragment of a multispecific antibody, or (ii) a biologically functional fragment of a therapeutic antibody.

16. The method of claim 14, wherein said therapeutic antibody or fragment thereof is selected from the group consisting of anti-HER2 antibodies anti-CD20 antibodies; anti-IL-8 antibodies; anti-VEGF antibodies; anti-CD40 antibodies, anti-CD 11a antibodies; anti-CD18 antibodies; anti-IgE antibodies; anti-Apo-2 receptor antibodies; anti-Tissue Factor (TF) antibodies; anti-human $\alpha_4\beta_7$ integrin antibodies; anti-EGFR antibodies; anti-CD3 antibodies; anti-CD25 antibodies; anti-CD4 antibodies; anti-CD52 antibodies; anti-Fc receptor antibodies; anti-carcinoembryonic antigen (CEA) antibodies; antibodies directed against breast epithelial cells; antibodies that bind to colon carcinoma cells; anti-CD38 antibodies; anti-CD33 antibodies; anti-CD22 antibodies; anti-EpCAM antibodies; anti-GpIIb/IIIa antibodies; anti-RSV antibodies; anti-CMV antibodies; anti-HIV antibodies; anti-hepatitis antibodies; anti-CA 125 antibodies; anti-$\alpha_V\beta_3$ antibodies; anti-human renal cell carcinoma antibodies; anti-human 17-1A antibodies; anti-human colorectal tumor antibodies; anti-human melanoma antibody R24 directed against GD3 ganglioside; anti-human squamous-cell carcinoma; and anti-human leukocyte antigen (HLA) antibodies, and anti-HLA DR antibodies.

17. The method of claim 14, wherein said therapeutic antibody or fragment thereof, is an antibody binding to:

(a) a HER receptor, and wherein, optionally, the HER receptor is HER2 and said therapeutic antibody comprises a heavy and/or light chain variable domain sequence selected from the group consisting of SEQ ID NOS: 16, 17, 18, and 19;

(b) VEGF, and wherein, optionally, said therapeutic antibody comprises a heavy and/or light chain variable domain sequence selected from the group consisting of SEQ ID NOS: 20 through 25;

(c) IgE;

(d) CD20, and wherein, optionally, said therapeutic antibody comprises a heavy and/or light chain variable domain sequence selected from the group consisting of SEQ ID NOS: 1 through 15;

(e) CD11a, and wherein, optionally, said therapeutic antibody comprises a heavy and/or light chain variable domain sequence selected from the group consisting of SEQ ID NOS: 26 through 29;

(f) CD40; or

(g) DR5, and wherein, optionally, said therapeutic antibody is selected from the group consisting of Apomabs 1.1, 2.1, 3.1, 4.1, 5.1, 5.2, 5.3, 6.1, 6.2, 6.3, 7.1, 7.2, 7.3, 8.1, 8.3, 9.1, 1.2, 2.2, 3.2, 4.2, 5.2, 6.2, 7.2, 8.2, 9.2, 1.3, 2.2, 3.3, 4.3, 5.3, 6.3, 7.3, 8.3, 9.3, and 25.3.

18. The method of any one of claims 1 to 17 wherein said recombinant host cell is (i) an eukaryotic host cell, or (ii) a prokaryotic host cell.

19. The method of claim 18 wherein said eukaryotic host cell is a mammalian host cell and, optionally, is a Chinese Hamster Ovary (CHO) cell, or said prokaryotic host cell is a bacterial cell and, optionally, is an *E. coli* cell.

20. The method according to claim 1, wherein the air sparging maintains the HCCF at 100% to 30% saturated with air.

21. A method for the prevention of the reduction of a disulfide bond of an antibody expressed by a recombinant eukaryotic host cell, comprising decreasing the level of an enzyme of the Trx system in the eukaryotic host cell, whereby the reduction of the disulfide bond of the antibody is prevented in the pre-harvest cell culture fluid (CFF) or harvested cell culture fluid (HCCF).

22. The method according to claim 21, wherein the enzyme is thioredoxin reductase, G6PD or hexokinase.

23. The method according to claim 22, wherein the enzyme level is decreased by a nucleic acid molecule comprising an antisense nucleotide.

24. The method according to claim 22, wherein the enzyme level is decreased by an interfering RNA.

25. The method according to claim 24, wherein the enzyme level is decreased by use of a siRNA.

26. The method according to claim 23 or 25 wherein said siRNA or antisense nucleotide specifically binds a thioredoxin reductase gene sequence.

27. The method according to claim 26 wherein the thioredoxin reductase gene sequence is a CHO thioredoxin reductase gene sequence.

28. The method according to claim 21 wherein the eukaryotic host cell is a mammalian host cell.

29. The method according to claim 28 wherein the mammalian host cell is Chinese Hamster Ovary (CHO) cell.

30. The method according to claim 21, wherein the antibody is a therapeutic antibody.

WHAT IS CLAIMED:

1. A method for the prevention of the reduction of a disulfide bond in a polypeptide expressed in a recombinant host cell, comprising supplementing the pre-harvest or harvested culture fluid of said recombinant host cell with a thioredoxin inhibitor.

2. The method of claim 1 wherein said thioredoxin inhibitor is added to the pre-harvest culture fluid.

3. The method of claim 1 wherein said thioredoxin inhibitor is added to the harvested culture fluid.

4. The method of claim 1 wherein said thioredoxin inhibitor is a direct inhibitor of thioredoxin.

5. The method of claim 4 wherein said thioredoxin inhibitor is an alkyl-2-imidazolyl disulfide or a naphthoquinone spiroketal derivative.

6. The method of claim 1 wherein said thioredoxin inhibitor is a specific inhibitor of thioredoxin reductase.

7. The method of claim 6 wherein said thioredoxin inhibitor is a gold complex.

8. The method of claim 7 wherein said gold complex is aurothioglucose (ATG) or aurothiomalate (ATM).

9. The method of claim 8 wherein said ATG or said ATM is added in a concentration between about 0.1 mM and about 1 mM.

10. The method of claim 8 wherein said ATG or said ATM is added at a concentration at least about four-times of thioredoxin reductase concentration in said pre-harvest or harvested culture fluid.

11. The method of claim 1 wherein said thioredoxin inhibitor is a metal ion.

12. The method of claim 11 wherein said metal ion is selected from the group consisting of Hg^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+}, and Mn^{2+}.

13. The method of claim 12 wherein said metal ion is Cu^{2+} present in the form of cupric sulfate.

14. The method of claim 13 wherein said cupric supfate is in the form of pentrahydrate or in anhydrous form.

15. The method of claim 13 wherein said cupric sulfate is added in a concentration between about 5 μM and about 100 μM.

16. The method of claim 13 wherein said cupric sulfate is added in a concentration between about 10 μM to about 80 μM.

17. The method of claim 13 wherein said cupric sulfate is added in a concentration between about 15 μM and about 50 μM.

18. The method of claim 13 wherein said cupric sulfate is added at a concentration at least about two-times of thioredoxin concentration in said pre-harvest or harvested culture fluid.

19. The method of claim 1 wherein said thioredoxin inhibitor is as inhibitor of G6PD.

20. The method of claim 19 wherein said thioredoxin inibitor is selected from the group consisting of pyridoxal 5'-phosphate, 1 fluoro-2,4 dinitrobenzene, dehydroepiandrosterone (DHEA) and epiandrosterone (EA).

21. The method of claim 20 wherein said DHEA is added in a concentration between about 0.05 mM and about 5 mM.

22. The method of claim 20 wherein said DHEA is added in a concentration between about 0.1 mM and about 2.5 mM.

23. The method of claim 1 wherein said thioredoxin inhibitor is an inhibitor of hexokinase activity.

24. The method of claim 23 wherein said thioredoxin inhibitor is a chelator of metal ions.

25. The method of claim 24 wherein said chelator of metal ions is ethylenediamine tetraacetic acid (EDTA).

26. The method of claim 25 wherein said EDTA is added in a concentration between about 5 mM and about 60 mM.

27. The method of claim 25 wherein said EDTA is added in a concentration between about 10 mM and about 50 mM.

28. The method of claim 25 wherein said EDTA is added in a concentration between about 20 mM and about 40 mM.

29. The method of claim 23 wherein said thioredoxin inhibitor is selected from the group consisting of sorbose-1-phosphate, polyphosphates; 6-deoxy-6-fluoroglucose, 2-C-hydroxy-methylglucose, xylose, and lyxose.

30. The method of claim 1 wherein said thioredoxin inhibitor is cystine, cysteine, or oxidized glutathione.

31. The method of claim 30 wherein said cystine, cysteine or oxidized glutathione is added at a concentration at least about 40-times of the concentration of said polypeptide in said pre-harvest or harvested culture fluid.

32. The method of claim 1 wherein said thiodedoxin inhibitor is a siRNA, antisense nucleotide, or antibody specifically binding to a thioredoxin reductase.

33. The method of claim 1 wherein said thioredoxin inhibitor is a measure indirectly resulting in the inhibition of thioredoxin activity.

34. The method of claim 33 wherein said measure is air sparging the harvested culture fluid of said recombinant host cell.

35. The method of claim 33 wherein said measure is lowering the pH of the harvested culture fluid of said recombinant host cells.

36. The method of any one of claims 1 to 33 further comprising the step of air sparging the harvested culture fluid of said recombinant host cell.

37. The method of any one of claims 1 to 33 further comprising the step of lowering the pH of the harvested culture fluid of said recombinant host cells.

38. The method of claim 1 wherein said polypeptide is an antibody, or a biologically functional fragment of an antibody.

39. The method of claim 38 wherein said antibody fragment is selected from the group consisting of Fab, Fab', $F(ab')_2$, scFv, $(scFv)_2$, dAb, complementarity determining region (CDR) fragments, linear antibodies, single-chain antibody molecules, minibodies, diabodies, and multispecific antibodies formed from antibody fragments.

40. The method of claim 38 wherein said antibody or antibody fragment is a therapeutic antibody or a biologically functional fragment thereof.

41. The method of claim 40 wherein said therapeutic antibody is selected from the group consisting of anti-HER2 antibodies anti-CD20 antibodies; anti-IL-8 antibodies; anti-VEGF antibodies; anti-CD40 antibodies, anti-CD11a antibodies; anti-CD18 antibodies; anti-IgE antibodies; anti-Apo-2 receptor antibodies; anti-Tissue Factor (TF) antibodies; anti-human $\alpha_4\beta_7$ integrin antibodies; anti-EGFR antibodies; anti-CD3 antibodies; anti-CD25 antibodies; anti-CD4 antibodies; anti-CD52 antibodies; anti-Fc receptor antibodies; anti-carcinoembryonic antigen (CEA) antibodies; antibodies directed against breast epithelial cells; antibodies that bind

to colon carcinoma cells; anti-CD38 antibodies; anti-CD33 antibodies; anti-CD22 antibodies; anti-EpCAM antibodies; anti-GpIIb/IIIa antibodies; anti-RSV antibodies; anti-CMV antibodies; anti-HIV antibodies; anti-hepatitis antibodies; anti-CA 125 antibodies; anti-αvβ3 antibodies; anti-human renal cell carcinoma antibodies; anti-human 17-1A antibodies; anti-human colorectal tumor antibodies; anti-human melanoma antibody R24 directed against GD3 ganglioside; anti-human squamous-cell carcinoma; and anti-human leukocyte antigen (HLA) antibodies, and anti-HLA DR antibodies.

42. The method of claim 40 wherein said therapeutic antibody is an antibody binding to a HER receptor, VEGF, IgE, CD20, CD11a, CD40, or DR5.

43. The method of claim 42 wherein said HER receptor is HER1 and/or HER2.

44. The method of claim 43 wherein the HER receptor is HER2.

45. The method of claim 44 wherein said therapeutic antibody comprises a heavy and/or light chain variable domain sequence selected from the group consisting of SEQ ID NOS: 16, 17, 18, and 19.

46. The method of claim 42 wherein said therapeutic antibody is an antibody that binds to CD20.

47. The method of claim 46 wherein said therapeutic antibody comprises a heavy and/or light chain variable domain sequence selected from the group consisting of SEQ ID NOS: 1 through 15.

48. The method of claim 42 wherein said therapeutic antibody is an antibody that binds to VEGF.

49. The method of claim 48 wherein said therapeutic antibody comprises a heavy and/or light chain variable domain sequence selected from the group consisting of SEQ ID NOS: 20 through 25.

50. The method of claim 42 wherein said therapeutic antibody is an antibody that binds CD11a.

51. The method of claim 50 wherein said therapeutic antibody comprises a heavy and/or light chain variable domain sequence selected from the group consisting of SEQ ID NOS: 26 through 29.

52. The method of claim 42 wherein said therapeutic antibody binds to a DR5 receptor.

53. The method of claim 52 wherein said therapeutic antibody is selected from the group consisting of Apomabs 1.1, 2.1, 3.1, 4.1, 5.1, 5.2, 5.3 , 6.1, 6.2, 6.3, 7.1, 7.2, 7.3,8.1, 8.3, 9.1, 1.2, 2.2, 3.2, 4.2, 5.2, 6.2, 7.2, 8.2, 9.2, 1.3, 2.2, 3.3, 4.3, 5.3, 6.3, 7.3, 8.3, 9.3, and 25.3.

54. The method of claim 52 wherein said therapeutic antibody is Apomab 8.3 or Apomab 7.3.

55. The method of claim 54 wherein said therapeutic antibody is Apomab 7.3.

56. The method of claim 1 wherein said polypeptide is a therapeutic polypeptide.

57. The method of claim 56 wherein said therapeutic polypeptide is selected from the group consisting of a growth hormone, including human growth hormone and bovine growth hormone; growth hormone releasing factor; parathyroid hormone; thyroid stimulating hormone; lipoproteins; alpha-1-antitrypsin; insulin A-chain; insulin B-chain; proinsulin; follicle stimulating hormone; calcitonin; luteinizing hormone; glucagon; clotting factors such as factor VIIIC, factor IX, tissue factor, and von Willebrands factor; anti-clotting factors such as Protein C; atrial natriuretic factor; lung surfactant; a plasminogen activator, such as urokinase or human urine or tissue-type plasminogen activator (t-PA); bombesin; thrombin; hemopoietic growth factor; tumor necrosis factor-alpha and -beta; enkephalinase; RANTES (regulated on activation normally T-cell expressed and secreted); human macrophage inflammatory protein (MIP-1-alpha); a serum albumin such as human serum albumin; Muellerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; a

microbial protein, such as beta-lactamase; DNase; IgE; a cytotoxic T-lymphocyte associated antigen (CTLA), such as CTLA-4; inhibin; activin; vascular endothelial growth factor (VEGF); receptors for hormones or growth factors; Protein A or D; rheumatoid factors; a neurotrophic factor such as bone-derived neurotrophic factor (BDNF), neurotrophin-3, -4, -5, or -6 (NT-3, NT-4, NT-5, or NT-6), or a nerve growth factor such as NGF-β; platelet-derived growth factor (PDGF); fibroblast growth factor such as aFGF and bFGF; epidermal growth factor (EGF); transforming growth factor (TGF) such as TGF-alpha and TGF-beta, including TGF-β1, TGF-β2, TGF-β3, TGF-β4, or TGF-β5; insulin-like growth factor-I and -II (IGF-I and IGF-II); des(1-3)-IGF-I (brain IGF-I), insulin-like growth factor binding proteins; CD proteins such as CD3, CD4, CD8, CD19, CD20, CD34, and CD40; erythropoietin; osteoinductive factors; immunotoxins; a bone morphogenetic protein (BMP); an interferon such as interferon-alpha, -beta, and -gamma; colony stimulating factors (CSFs), *e.g.*, M-CSF, GM-CSF, and G-CSF; interleukins (ILs), *e.g.*, IL-1 to IL-10; superoxide dismutase; T-cell receptors; surface membrane proteins; decay accelerating factor; viral antigen such as, for example, a portion of the AIDS envelope; transport proteins; homing receptors; addressins; regulatory proteins; integrins such as CD11a, CD11b, CD11c, CD18, an ICAM, VLA-4 and VCAM; a tumor associated antigen such as HER2, HER3 or HER4 receptor; and fragments of said polypeptides.

58. The method of claim 1 wherein said recombinant host cell is an eukaryotic host cell.

59. The method of claim 58 wherein said eukaryotic host cell is a mammalian host cell.

60. The method of claim 59 wherein said mammalian host cell is a Chinese Hamster Ovary (CHO) cell.

61. The method of claim 1 wherein the recombinant host cell is a prokaryotic host cell.

62. The method of claim 61 wherein the prokaryotic host cell is a bacterial cell.

63. The method of claim 62 wherein the bacterial cell is an *E. coli* cell.