~~CELL CULTURE IMPROVEMENTS~~

METHODS OF PRODUCING ANTI-TNF-ALPHA ANTIBODIES IN MAMMALIAN CELL CULTURE

Related applications

This application claims the benefit of priority to U.S. Provisional Application No. 60/845158, filed on September 13, 2006, and U.S. Provisional Application No. 60/876374, filed on December 21, 2006. The contents of each of the above priority documents is incorporated by reference herein.

Background of the invention

Recombinant DNA technology has provided a means to produce proteins in amounts which allow for their use in a spectrum of applications, including therapeutic, diagnostic, agricultural, and research purposes.

One goal of recombinant protein production is the optimization of cell culture media and conditions in order to obtain the greatest amount of protein and the most efficient means of productivity. Any improvement, including incremental improvements, can have enormous benefits economically. In the pharmaceutical industry, optimization of protein production for biologics used in therapies for the treatment of disease is advantageous, as any improvement can have significant impact when the biologic is manufactured on a large scale. As such, there remains a need to maximize protein production from cell cultures expressing biologic proteins for use in medicine.

Typically mammalian cell culture media is based on commercially available media formulations, including, for example, DMEM or Ham's F12. Often media formulations are not sufficiently enriched to support increases in both cell growth and biologic protein expression. There remains a need for improved cell culture media, supplements, and cell culture methods for improved protein production.

Summary of the invention

The invention provides methods and compositions for improving protein expression in cell culture, particularly mammalian cell culture. The invention relates to improved cell culture media, including media for growing cells for protein expression and cell culture production media optimized for protein expression.

What is claimed:

1. A serum-free cell culture medium comprising Part A, Part B, and Part C, wherein
   a) Part A consists essentially of a modified basal medium which excludes the following components: sodium bicarbonate, a buffer, mono-basic sodium phosphate, di-basic sodium phosphate, an osmolarity regulator, a surfactant, and monosaccharide glucose;
   b) Part B consists essentially of an inorganic iron source; and
   c) Part C comprises a recombinant growth factor; a buffer; an osmolarity regulator; an energy source; and at least two different non-animal hydrolysates.

2. The cell culture medium of claim 1, wherein Part A further comprises non-ferrous metal ions, vitamins, or a combination of both.

3. The cell culture medium of claim 1, wherein the inorganic iron source of Part B is ferric citrate.

4. The cell culture medium of claim 3, comprising about 122.5 mg/L or 0.5 mM final solution concentration ferric citrate.

5. The cell culture medium of claim 1, wherein the recombinant growth factor of Part C is selected from the group consisting of insulin or a recombinant analog, IGF-1, and a combination of insulin and IGF-1.

6. The cell culture medium of claim 5, comprising about 4 mg/L to 13mg/L insulin, or a recombinant analog thereof.

7. The cell culture medium of claim 1, wherein the buffer which is excluded from the modified basal medium is HEPES buffer.

8. The cell culture medium of claim 1, wherein the buffer of Part C comprises a phosphate buffer, HEPES, and sodium bicarbonate.

9. The cell culture medium of claim 8, comprising about 1.6g/L of sodium bicarbonate.

10. The cell culture medium of claim 8, comprising about 1.8g/L HEPES.

11. The cell culture medium of claim 8, wherein the phosphate buffer comprises about 0.01 to 0.5 g/L mono- and di-basic sodium phosphates.

12. The cell culture medium of claim 1, wherein Part C further comprises asparagine, glutamine, or glutamine and asparagine.

13. The cell culture medium of claim 1, wherein the osmolarity regulator of Part C is NaCl.

14. The cell culture medium of claim 13, comprising about 1.0 to 6.5 g/L NaCl.

15. The cell culture medium of claim 1, wherein the energy source of Part C is a monosaccharide.

16. The cell culture medium of claim 15, wherein the monosaccharide is selected from the group consisting of glucose, maltose, mannose, galactose and fructose.

17. The cell culture medium of claim 16, wherein the glucose is D-glucose.

18. The cell culture medium of claim 17, comprising no greater than about 7.0 g/L glucose.

19. The cell culture medium of claim 1, wherein the least two different non-animal based hydrolysates of Part C are a plant-based hydrolysate and a hydrolysate which is neither animal or plant-based.

20. The cell culture medium of claim 19, wherein the plant-based hydrolysate is a soy-based hydrolysate.

21. The cell culture medium of claim 19, wherein the hydrolysate which is neither animal or plant-based is a yeast-based hydrolysate.

22. The cell culture medium of any one of claims 1-21, further comprising methotrexate.

23. The cell culture medium of claim 22, comprising about 100nM to 5000 nM methotrexate.

24. The cell culture medium of any one of claims 1-21, further comprising a cell protectant or surfactant.

25. The cell culture medium of claim 24, wherein the surfactant is methyl cellulose or a pluronic polyol.

26. The cell culture medium of claim 25, wherein the pluronic polyol is Pluronic F-68.

27. The cell culture medium of claim 26, comprising about 1.0 g/L Pluronic F-68.

28. The cell culture medium of any one of claims 1-21, further comprising L-glutamine.

29. The cell culture medium of any one of claims 1-21, wherein the pH ranges from 7.1 to 7.3.

30. The cell culture medium of any one of claims 1-21, wherein the osmolarity ranges from 320 to 450 mOsm/kg.

31. A method for producing a protein comprising culturing a mammalian cell in the cell culture medium of any one of claims 1-21.

32. The method of claim 31, wherein the mammalian cell is a Chinese Hamster Ovary (CHO) cell.

33. The method of claim 31 or 32, wherein the protein is an antibody.

34. The method of claim 33, wherein the antibody is selected from the group consisting of an anti-TNFα antibody, an anti-IL-12 antibody, an anti-IL-18 antibody, and an anti-EPO receptor (EPO-R) antibody.

35. A serum-free cell culture medium comprising:

a) a basal medium;

b) about 8-12 ml/kg or 116-126 mg/L ferric citrate;

c) about 2-6 mg/kg recombinant human insulin;

d) about 2-5 g/kg anhydrous glucose;

e) about 0.1 – 0.5 g/kg L-glutamine;

f) about 1-3 g/kg sodium bicarbonate;

g) about 0.01-0.05 g/kg $NaH_2PO_4 \cdot H_2O$;

h) about 0.4 to 0.5 g/kg of $Na_2HPO_4 \cdot 7H_2O$; and

i) about 1.0-3.0 g/kg yeast-based hydrolysate.

36. The cell culture medium of claim 35, comprising

a) a basal medium;

b) about 10.0 ml/kg or 122 mg/L ferric citrate;

c) about 4.0 mg/kg recombinant human insulin;

d) about 3.5 g/kg anhydrous glucose;

e) about 0.29 g/kg L-glutamine;

f) about 1.6 g/kg sodium bicarbonate;

g) about 0.03 g/kg $NaH_2PO_4 \cdot H_2O$;

h) about 0.43 to 0.44 g/kg of $Na_2HPO_4 \cdot 7H_2O$; and

i) about 2.0 g/kg yeast-based hydrolysate.

37. The cell culture medium of claim 35 or 36, further comprising about 2.50 mL/kg methotrexate.

38. A method for producing a protein comprising

a) culturing mammalian cells comprising a nucleic acid encoding the protein in the culture medium of claim 35 or 36; and

b) transferring the culture of (a) into a cell culture production medium,

such that the protein is produced.

39. The method of claim 38, further comprising isolating the protein from the cell culture production medium.

40. The method of claim 38, wherein the protein is an antibody.

41. The method of claim 40, wherein the antibody is D2E7 (adalimumab).

42. A serum-free cell culture production medium comprising:

a) a modified basal medium which excludes the following components sodium bicarbonate, buffer, mono-basic sodium phosphate, di-basic sodium phosphate, an osmolarity regulator, a surfactant, and monosaccharide glucose;

b) about 8 to12 ml/kg or 122.45 mg/L ferric citrate;

c) about 4 to 8 mL/kg or 10 to 14 mg/kg recombinant human insulin;

d) about 5 to 9 g/kg anhydrous glucose;

e) about 0.5 to 0.7 g/kg L-glutamine;

f) about 1 to 2 g/kg sodium bicarbonate;

g) about 1 to 2 g/kg HEPES;

h) about 2 to 3 g/kg NaCl;

i) about 0.5 to 2 g/kg Pluronic F-68;

j) about 0.01 to 0.1 g/kg $NaH_2PO_4 \cdot H_2O$;

k) about 0.4 to 0.5 g/kg $Na_2HPO_4 \cdot 7H_2O$;

l) about 8 to 12 g/kg yeast-based hydrolysate; and

m) about 60 to 70 g/kg plant-based hydrolysate.

43. The cell culture production medium of claim 42, wherein the cell culture medium comprises

a) about 10.0 ml/kg or 122.45 mg/L ferric citrate;

b) about 6.0 mL/kg or 12 mg/kg recombinant human insulin;

c) about 7.0 g/kg anhydrous glucose;

d) about 0.58 to 0.59 g/kg L-glutamine;

e) about 1.6 g/kg sodium bicarbonate;

f) about 1.8 g/kg HEPES;

g) about 2.4 to 2.5 g/kg NaCl;

h) about 1.0 g/kg Pluronic F-68;

i) about 0.03 to 0.04 g/kg $NaH_2PO_4 \cdot H_2O$;

j) about 0.43 to 0.44 g/kg $Na_2HPO_4 \cdot 7H_2O$;

k) about 10.7 g/kg yeast-based hydrolysate; and

l) about 6.9 to 7.0 g/kg plant-based hydrolysate.

44. The cell culture production medium of claim 42 or 43, having a pH of about 7.10 to 7.20.

45. The cell culture production medium of claim 42 or 43, having an osmolality of about 373 to 403 mOsm/kg.

46. A serum-free cell culture medium comprising:

a) a modified basal medium, which excludes the following components sodium bicarbonate, buffer, mono-basic sodium phosphate, di-basic sodium phosphate, an osmolarity regulator, a surfactant, and monosaccharide glucose;

b) about 8 to12 ml/kg or 122.45 mg/L ferric citrate;

c) about 3 to 5 mL/kg or 6 to 8 mg/kg recombinant human insulin;

d) about 5 to 9 g/kg anhydrous glucose;

e) about 0.1 to 2 g/kg L-glutamine;

f) about 1 to 2 g/kg sodium bicarbonate;

g) about 1 to 2 g/kg HEPES;

h) about 2 to 3 g/kg NaCl;

i) about 0.1 to 2 g/kg Pluronic F-68;

j) about 0.01 to 0.1 g/kg $NaH_2PO_4 \cdot H_2O$;

k) about 0.4 to 0.5 g/kg $Na_2HPO_4 \cdot 7H_2O$;

l) about 0.4 to 0.5 g/kg L-asparagine monohydrate;

m) about 2 to 6 g/kg yeast-based hydrolysate; and

n) about 2 to 4 g/kg plant-based hydrolysate.

47. The cell culture medium of claim 46, wherein the cell culture medium comprises

a) about 10.0 ml/kg or 122.45 mg/kg ferric citrate;

b) about 3.8 to 3.9 mL/kg or 7.8 mg/kg recombinant human insulin;

c) about 7.0 g/kg anhydrous glucose;

d) about 0.8 to 0.9 g/kg L-glutamine;

e) about 1.6 g/kg sodium bicarbonate;

f) about 1.8 g/kg HEPES;

g) about 2.6 to 2.7 g/kg NaCl;

h) about 1.0 g/kg Pluronic F-68;

i) about 0.03 to 0.04 g/kg $NaH_2PO_4 \cdot H_2O$;

j) about 0.43 to 0.44 g/kg $Na_2HPO_4 \cdot 7H_2O$;

k) about 0.45 g/kg L-asparagine monohydrate;

l) about 4.0 g/kg yeast-based hydrolysate; and

m) about 2.6 g/kg plant-based hydrolysate.

48. The cell culture medium of any one of claims 42-27, further comprising about 2.50 mL/kg methotrexate

49. A method for producing a protein comprising culturing a mammalian cell comprising a nucleic acid encoding the antibody in the cell culture medium of any one of claims 42-47.

50. The method of claim 49, wherein the mammalian cell is a CHO cell.

51. The method of claim 49, wherein the protein is an antibody.

52. The method of claim 51, wherein the antibody is an anti-TNFα antibody or an anti-EPO-R antibody.

53. The method of claim 52, wherein the anti-TNFα antibody is a fully human anti-TNFα antibody.

54. The method of claim 53, wherein the fully human anti-TNFα antibody is D2E7 (adalimumab).

55. A serum-free cell culture medium comprising:

a) a modified basal medium, which excludes the following components sodium bicarbonate, buffer, mono-basic sodium phosphate, di-basic sodium phosphate, an osmolarity regulator, a surfactant, and monosaccharide glucose;

b) about 8 to 10 ml/kg or 120 to 130 mg/L ferric citrate;

c) about 3 to 5 mL/kg or 7.8 mg/kg recombinant human insulin;

d) about 5 to 9 g/kg anhydrous glucose;

e) about 0.8 to 0.9 g/kg L-glutamine;

f) about 0.3 to 0.5 g/kg L-asparagine monohydrate;

g) about 1 ot 2 g/kg sodium bicarbonate

h) about 1 to 2 g/kg HEPES;

i) about 2 to 3 g/kg NaCl;

j) about 0.5 to 2 g/kg Pluronic F-68;

k) about 0.01 to 0.1 g/kg $NaH_2PO_4 \cdot H_2O$;

l) about 0.1 to 1.0 g/kg $Na_2HPO_4 \cdot 7H_2O$;

m) about 2 to 6 g/kg yeast-based hydrolysate; and

n) about 2 to 4 g/kg plant-based hydrolysate.

56. The cell culture medium of claim 55, comprising

a) about 10 ml/kg or 122 mg/L ferric citrate;

b) about 3.8 to 3.9 mL/kg or 7.8 mg/kg recombinant human insulin;

c) about 7.0 g/kg anhydrous glucose;

d) about 0.87 to 0.88 g/kg L-glutamine;

e) about 0.45 g/kg L-asparagine monohydrate;

f) about 1.6 g/kg sodium bicarbonate

g) about 1.8 g/kg HEPES;

h) about 2.67 to 2.68 g/kg NaCl;

i) about 1.0 g/kg Pluronic F-68;

j) about 0.03 to 0.04 g/kg $NaH_2PO_4 \cdot H_2O$;

k) about 0.43 to 0.44 g/kg $Na_2HPO_4 4 \cdot 7H_2O$;

l) about 4.0 g/kg yeast-based hydrolysate; and

m) about 2.6 g/kg plant-based hydrolysate.

57. The cell culture medium of claim 55 or 56, further comprising methotrexate.

58. A serum-free cell culture medium comprising:

a) basal cell growth medium;

b) about 8 to 12 ml/kg or 120 to 130 mg/L ferric citrate;

c) about 2 to 6 mg/kg recombinant human insulin;

d) about 150 to 250 g/kg anhydrous glucose;

e) about 0.1 to 0.5 g/kg L-glutamine;

f) about 1 to 2 g/kg sodium bicarbonate; and

g) about 5 to 15 g/kg yeast-based hydrolysate.

59. The cell culture medium of claim 58, comprising

a) about 10 ml/kg or 122.45 mg/L ferric citrate;

b) about 4 mg/kg recombinant human insulin;

c) about 200 g/kg anhydrous glucose;

d) about 0.29 to 0.30 g/kg L-glutamine;

e) about 1.6 g/kg sodium bicarbonate; and

f) about 11 g/kg yeast-based hydrolysate.

60. The cell culture medium of claim 58 or 59, further comprising methotrexate.

61. A method of producing a protein comprising culturing a mammalian cell comprising a nucleic acid encoding the protein in a cell culture medium of any one of claims 55-60.

62. The method of claim 61, wherein the protein is an antibody.

63. The method of claim 62, wherein the mammalian cell is a CHO cell.

64. The method of claim 63, wherein the nucleic acid encodes a fully human, anti-IL-12 antibody.

65. The method of claim 64, wherein the fully human, anti-IL-12 antibody is ABT-874.

66. A serum-free cell culture medium comprising:

a) basal cell growth medium;

b) about 8 to 12 ml/kg or 120 to 130 mg/L ferric citrate;

c) about 2 to 6 mg/kg recombinant human insulin;

d) about 1 to 3 g/kg anhydrous glucose;

e) about 0.1 to 1 g/kg L-glutamine;

f) about 1 to 2 g/kg sodium bicarbonate; and

g) about 1 to 4 g/kg yeast-based hydrolysate.

67. The cell culture medium of claim 66, comprising

a) about 10 ml/kg or 122.45 mg/L ferric citrate;

b) about 4 mg/kg recombinant human insulin;

c) about 1.5 g/kg anhydrous glucose;

d) about 0.29 to 0.30 g/kg L-glutamine;

e) about 1.6 g/kg sodium bicarbonate; and

f) about 2 g/kg yeast-based hydrolysate.

68. The cell culture medium of claim 66 or 67, further comprising methotrexate.

69. The cell culture medium of claim 66 or 67, having a pH of about 7.10 to 7.30.

70. The cell culture medium of claim 66 or 67, having an osmolality of about 300 to 340 mOsm/kg.

71. The cell culture medium of claim 66 or 67, comprising at least 8 g/kg yeast-based hydrolysate.

72. A method of producing a protein comprising culturing a mammalian cell comprising a nucleic acid encoding the antibody in the cell culture medium of any one of claims 62-65.

73. The method of claim 72, wherein the protein is an antibody.

74. The method of claim 72, wherein the mammalian cell is a CHO cell.

75. The method of claim 72, wherein the nucleic acid encodes an anti-IL-12 antibody or an anti-EPO-R antibody.

76. The method of claim 75, wherein the fully human, anti-IL-12 antibody is ABT-874.

77. A cell culture medium comprising:

a) a modified basal medium which excludes the following components sodium bicarbonate, buffer, mono-basic sodium phosphate, di-basic sodium phosphate, an osmolarity regulator, a surfactant, and monosaccharide glucose;

b) about 8 to12 ml/kg or 120 to 130 mg/L ferric citrate;

c) about 2.5 to 4.5 mL/kg or 7.8 mg/kg recombinant human insulin;

d) about 5 to 9 g/kg anhydrous glucose;

e) about 0.5 to 1 g/kg L-glutamine;

f) about 0.1 to 1 g/kg L-asparagine monohydrate;

g) about 1 to 2 g/kg sodium bicarbonate

h) about 1 to 2 g/kg HEPES;

i) about 1 to 4 g/kg NaCl;

j) about 0.1 to 2 g/kg Pluronic F-68;

k) about 0.01 to 0.1 g/kg $NaH_2PO_4 \cdot H_2O$;

l) about 0.1 to 1 g/kg $Na_2HPO_4 \cdot 7H_20$;

m) about 2 to 6 g/kg yeast-based hydrolysate; and

n) about 2 to 6 g/kg plant-based hydrolysate.

78. The cell culture medium of claim 77, comprising

a) about 10 ml/kg or 122.45 mg/L ferric citrate;

b) about 3.8 to 3.9 mL/kg or 7.8 mg/kg recombinant human insulin;

c) about 7.0 g/kg anhydrous glucose;

d) about 0.87 to 0.88 g/kg L-glutamine;

e) about 0.45 g/kg L-asparagine monohydrate;

f) about 1.6 g/kg sodium bicarbonate

g) about 1.8 g/kg HEPES;

h) about 2.67 g/kg NaCl;

i) about 1.0 g/kg Pluronic F-68;

j) about 0.03 to 0.04 g/kg $NaH_2PO_4 \cdot H_2O$;

k) about 0.43 to 0.44 g/kg $Na_2HPO_4 \cdot 7H_20$;

l) about 4.0 g/kg yeast-based hydrolysate; and

m) about 2.6 g/kg plant-based hydrolysate.

79. The cell culture medium of claim 77 or 78, having a pH of about 7.10 to 7.20.

80. The cell culture medium of claim 77 or 78, having an osmolality of about 373 to 403 mOsm/kg.

81. A cell culture production medium comprising:

a) a modified basal medium, which is modified to remove the following components sodium bicarbonate, HEPES buffer, mono-basic sodium phosphate, di-basic sodium phosphate, an osmolarity regulator, a surfactant, and monosaccharide glucose;

b) about 8 to 12 ml/kg or 120 to 130 mg/L ferric citrate;

c) about 4 to 8 mL/kg or 10 to 14 mg/kg recombinant human insulin;

d) about 5 to 9 g/kg anhydrous glucose;

e) about 0.1 to 1 g/kg L-glutamine;

f) about 1 to 2 g/kg sodium bicarbonate

g) about 1 to 2 g/kg HEPES;

h) about 1 to 3 g/kg NaCl;

i) about 0.5 to 2 g/kg Pluronic F-68;

j) about 0.01 to 0.1 g/kg $NaH_2PO_4 \cdot H_2O$;

k) about 0.1 to 1 g/kg $Na_2HPO_4 \cdot 7H_2O$;

l) about 8 to 12 g/kg yeast-based hydrolysate; and

m) about 6 to 8 g/kg plant-based hydrolysate.

82. The cell culture production medium of claim 81, comprising

a) about 10 ml/kg or 122.45 mg/L ferric citrate;

b) about 6.0 mL/kg or 12 mg/kg recombinant human insulin;

c) about 7.0 g/kg anhydrous glucose;

d) about 0.58 to 0.59 g/kg L-glutamine;

e) about 1.6 g/kg sodium bicarbonate

f) about 1.8 g/kg HEPES;

g) about 2.45 g/kg NaCl;

h) about 1.0 g/kg Pluronic F-68;

i) about 0.03 to 0.04 g/kg $NaH_2PO_4 \cdot H_2O$;

j) about 0.43 to 0.44 g/kg $Na_2HPO_4 \cdot 7H_2O$;

k) about 10.7 g/kg yeast-based hydrolysate; and

l) about 6.9 to 7.0 g/kg plant-based hydrolysate.

83. The cell culture production medium of claim 80 or 81, having a pH of about 7.10 to 7.20.

84. The cell culture production medium of claim 80 or 81, having an osmolality of about 373 to 403 mOsm/kg.

85. A cell culture production medium comprising:

a) a modified basal medium which excludes the following components sodium bicarbonate, buffer, mono-basic sodium phosphate, di-basic sodium phosphate, an osmolarity regulator, a surfactant, and monosaccharide glucose;

b) about 8 to 12 ml/kg or 110 to 130 mg/L ferric citrate;

c) about 4 to 8 mL/kg or 11 to 15 mg/kg recombinant human insulin;

d) about 5 to 9 g/kg anhydrous glucose;

e) about 0.1 to 1 g/kg L-glutamine;

f) about 1 to 2 g/kg sodium bicarbonate

g) about 1 to 2 g/kg HEPES;

h) about 1 to 3 g/kg NaCl;

i) about 0.1 to 2 g/kg Pluronic F-68;

j) about 0.01 to 0.1 g/kg $NaH_2PO_4 \cdot H_2O$;

k) about 0.1 to1 g/kg $Na_2HPO_4 \cdot 7H_2O$;

l) about 12 to 16 g/kg yeast-based hydrolysate; and

m) about 8 to 10 g/kg plant-based hydrolysate.

86. The cell culture production medium of claim 85, comprising

a) about 10 ml/kg or 122.45 mg/L ferric citrate;

b) about 6.5 mL/kg or 13 mg/kg recombinant human insulin;

c) about 7.0 g/kg anhydrous glucose;

d) about 0.58 to 0.59 g/kg L-glutamine;

e) about 1.6 g/kg sodium bicarbonate

f) about 1.8 g/kg HEPES;

g) about 2.45 g/kg NaCl;

h) about 1.0 g/kg Pluronic F-68;

i) about 0.03 to 0.04 g/kg $NaH_2PO_4 \cdot H_2O$;

j) about 0.43 to 0.44 g/kg $Na_2HPO_4 \cdot 7H_2O$;

k) about 14.2 to 14.3 g/kg yeast-based hydrolysate; and

l) about 9.2 to 9.3 g/kg plant-based hydrolysate.

87. The cell culture production medium of any one of claims 81-86, further comprising methotrexate.

88. A method of producing an antibody comprising culturing a mammalian cell comprising a nucleic acid encoding the antibody in a cell culture production medium of any one of claims 81-86.

89. The method of claim 88, wherein the mammalian cell is a CHO cell.

90. The method of claim 88, wherein the nucleic acid encodes an anti-IL-18 antibody.

91. The cell culture medium of any one of claims 35, 36, 42, 43, 46, 47, 55, 56, 77, 78, 81, 82, 85, or 86, wherein the plant-based hydrolysate is a soy-based hydrolysate.

92. A Chinese Hamster Ovary (CHO) cell in the cell culture medium of any one of claims 1-30, 35-37, 42-48, 55-60, 66-71, and 81-87..

93. A fed batch method of producing a protein comprising

a) culturing mammalian cells comprising a nucleic acid encoding the protein in a cell culture comprising a cell culture production medium; and

b) feeding the mammalian cells by adding a hydrolysate enrichment solution and a basal enrichment solution to the cell culture during a time period,

wherein the hydrolysate enrichment solution comprises at least two different non-animal-based hydrolysates,

such that the protein is produced.

94. The method of claim 93, wherein the basal enrichment solution comprises a concentrated basal medium.

95. The method of claim 93, wherein the basal enrichment solution comprises a basal medium, asparagine, and glucose.

96. The method of claim 94 or 95, wherein the basal medium is PF CHO.

97. The method of any one of claims 93-96, wherein the mammalian cell is a Chinese Hamster Ovary (CHO) cell.

98. The method of any one of claims 93-96, wherein the protein is an antibody.

99. The method of claim 98, wherein the antibody is selected from the group consisting of an anti-TNFα antibody, an anti-IL-12 antibody, an anti-IL-18 antibody, and an anti-EPO receptor (EPO-R) antibody.

100. The method of any one of claims 93-96, wherein the hydrolysate enrichment solution comprises a first hydrolysate which is not derived from a plant or an animal and a second plant-based hydrolysate.

101. The method of claim 100, wherein the hydrolysate which is not derived from a plant or an animal and a plant-based hydrolysate is a yeast-based hydrolysate.

102. The method of claim 101, wherein the plant-based hydrolysate is a soy-based hydrolysate

103. A fed batch method of producing an anti-TNFα antibody comprising

a) culturing Chinese Hamster Ovary (CHO) cells comprising a nucleic acid encoding the anti-TNFα antibody in a cell culture comprising a cell culture production medium; and

b) feeding the CHO cells by adding a hydrolysate enrichment solution and a basal enrichment solution to the cell culture during a time period,

wherein the basal enrichment solution comprises a basal medium, asparagine, and glucose, and

wherein the hydrolysate enrichment solution comprises at least two different non-animal-based hydrolysates,

such that the anti-TNFα antibody is produced.

104. A fed batch method of producing an anti-TNFα antibody comprising

a) culturing CHO cells comprising a nucleic acid encoding the anti-TNFα antibody in a cell culture comprising a cell culture production medium comprising at least 2.0 g/L of glucose, wherein the concentration of glucose is controlled by adding glucose to the cell culture production medium as required to maintain a concentration of at least 2.0 g/L of glucose; and

b) feeding the CHO cells by adding a hydrolysate enrichment solution and a basal enrichment solution to the cell culture during a time period,

wherein the basal enrichment solution comprises a basal medium, asparagine, and glucose, and

wherein the hydrolysate enrichment solution comprises at least two different non-animal-based hydrolysates,

such that the anti-TNFα antibody is produced.

105. The method of claim 103 or 104, further comprising recovering the anti-TNFα antibody.

106. The method of claim 103 or 104, wherein the cell culture is cultured at a temperature ranging from about 32 to 38 °C

107. The method of claim 106, wherein the culturing temperature is about 35 °C.

108. The method of claim 103 or 104, wherein the cell culture production medium is maintained between 20 and 65% dissolved oxygen.

109. The method of claim 108, wherein the cell culture production medium is maintained at about 30% dissolved oxygen.

110. The method of claim 103 or 104, wherein the osmolarity of the cell culture production medium is maintained throughout the culturing to no more than 500 mOsm.

111. The method of claim 103 or 104, wherein the hydrolysate enrichment solution comprises a first hydrolysate which is not derived from a plant or an animal and a second plant-based hydrolysate.

112. The method of claim 111, wherein the hydrolysate which is not derived from a plant or an animal and a plant-based hydrolysate is a yeast-based hydrolysate.

113. The method of claim 112, wherein the plant-based hydrolysate is a soy-based hydrolysate

114. The method of claim 103 or 104, wherein the hydrolysate enrichment solution consists essentially of about 50-280 g/kg of a soy-based hydrolysate and about 75-300 g/kg of a yeast-based hydrolysate.

115. The method of claim 103 or 104, wherein the basal medium is PF CHO.

116. The method of claim 103 or 104, wherein the basal enrichment solution has a pH of about 9.0 to 10.5.

117. The method of any one of claims 103-116, wherein the time period is between about 9 to 15 days.

118. The method of claim 117, wherein the time period is about 12 days.

119. The method of any one of claims 103-116, wherein the basal enrichment solution is added to the cell culture production medium on at least one of the following days of the time period: Day 4, Day 6, Day 9, and Day 11.

120. The method of any one of claims 103-116, wherein the hydrolysate enrichment solution is added to the cell culture production medium on Day 4, Day 7, or Day 4 and Day 7 of the time period

121 The method of any one of claims 103-116, further comprising adjusting the pH of the cell culture production medium according to a pH linear ramp, wherein the pH linear ramp comprises starting from a pH of about 7.1 to 7.2 and resulting in a final pH of about 6.9.

122. The method of claim 121, wherein the pH linear ramp is adjusted over a period of at least about 24 hours.

123. The method of claim 121, wherein the pH linear ramp is adjusted over a period of at least about 48 hours.

124. The method of claim 121, wherein the pH linear ramp is adjusted over a period of about 72 hours.

125. The method of claim 103 or 104, wherein the cell culture production medium comprises

a) a modified basal medium which excludes the following components sodium bicarbonate, buffer, mono-basic sodium phosphate, di-basic sodium phosphate, an osmolarity regulator, a surfactant, and monosaccharide glucose;

b) about 8 to 10 ml/kg or 110 to 130 mg/L ferric citrate;

c) about 4 to 8 mL/kg or 10 to 14 mg/kg recombinant human insulin;

d) about 5 to 9 g/kg anhydrous glucose;

e) about 0.1 to 1 g/kg L-glutamine;

f) about 1 to 3 g/kg sodium bicarbonate;

g) about 1 to 3 g/kg HEPES;

h) about 2 to 3 g/kg NaCl;

i) about 0.1 to 2 g/kg Pluronic F-68;

j) about 0.01 to 0.1 g/kg NaH_2PO_4-H_2O;

k) about 0.1 to 0.1 g/kg Na_2HPO_4-$7H_2O$;

l) about 8 to 12 g/kg yeast-based hydrolysate; and

m) about 6 to 8 g/kg plant-based hydrolysate.

126. The method of claim 125, wherein the cell culture production medium comprises

a) about 10.0 ml/kg or 122.45 mg/L ferric citrate;

b) about 6.0 mL/kg or 12 mg/kg recombinant human insulin;

c) about 7.0 g/kg anhydrous glucose;

d) about 0.58 to 0.59 g/kg L-glutamine;

e) about 1.6 g/kg sodium bicarbonate;

f) about 1.8 g/kg HEPES;

g) about 2.45 g/kg NaCl;

h) about 1.0 g/kg Pluronic F-68;

i) about 0.03 to 0.04 g/kg NaH_2PO_4-H_2O;

j) about 0.43 to 0.44 g/kg Na_2HPO_4-$7H_2O$;

k) about 10.7 g/kg yeast-based hydrolysate; and

l) about 6.9 to 7.0 g/kg plant-based hydrolysate.

127. The method of any one of claims 103-126, wherein the mammalian cell is a CHO cell.

128. The method of any one of claims 103-126, wherein the cell culture is a large scale cell culture.

129. The method of claim 128, wherein the large scale cell culture is greater than about 10 L.

130. The method of claim 128, wherein the large scale cell culture is 13 L.

131. The method of any one of claims 103-126, wherein the anti-TNFα antibody is a fully human anti-TNFα antibody.

132. The method of claim 131, wherein the anti-TNFα antibody is adalimumab.

133. A fed batch method of producing an anti-IL12 antibody comprising

a) culturing CHO cells comprising a nucleic acid encoding the antibody in a cell culture comprising a cell culture production medium,

b) feeding the CHO cells by adding a hydrolysate enrichment solution and a basal enrichment solution to the cell culture during a time period,

wherein the basal enrichment solution comprises a basal medium, asparagine, and glucose, and

wherein the hydrolysate enrichment solution comprises at least two different non-animal-based hydrosylates,

such that the anti-IL12 antibody is produced.

134. The method of claim 133, wherein the hydrolysate enrichment solution further comprises glucose.

135. The method of claim 133, further comprising recovering the anti-IL12 antibody.

136. The method of claim 133, wherein the cell culture is cultured at a temperature ranging from about 32 to 38 °C

137. The method of claim 133, wherein the culturing temperature is about 33°C.

138. The method of claim 133, wherein the cell culture production medium is maintained at between 20-65% dissolved oxygen

139. The method of claim 138, wherein the cell culture production medium is maintained at about 40% dissolved oxygen.

140. The method of claim 133, wherein the cell culture production medium has a pH of about 6.7 to 7.2.

141. The method of claim 133, wherein the hydrolysate enrichment solution comprises a hydrolysate which is not derived from a plant or an animal and a plant-based hydrolysate.

142. The method of claim 141, wherein the hydrolysate which is not derived from a plant or an animal is a yeast-based hydrolysate,

143. The method of claim 142, wherein the plant-based hydrolysate is a soy-based hydrolysate.

144. The method of claim 133, wherein the hydrolysate enrichment solution consists essentially of about 50-225 g/kg of a soy-based hydrolysate, about 75-300 g/kg of a yeast-based hydrolysate, and about 2 to 3 g/L glucose.

145. The method of claim 133, wherein the basal enrichment solution comprises a basal medium, asparagine, and glucose.

146. The method of claim 145, wherein the basal enrichment solution has a pH of about 9.7 and an osmolarity of about 1400 to 1500 mOsm.

147. The method of claim 145, wherein the basal medium in the basal enrichment solution is PF CHO.

148. The method of any one of claims 133-147, wherein the time period is between 14-15 days.

149. The method of any one of claims 133-147, wherein the basal enrichment solution is added to the cell culture production medium every other day beginning on day 5 of the time period.

150. The method of any one of claims 133-147, wherein the hydrolysate enrichment solution is added to the cell culture production medium every day beginning on day 6 of the time period.

151. The method of any one of claims 133-147, wherein the basal enrichment solution and the hydrolysate enrichment solution are added to the cell culture production medium every day beginning on day 5 of the time period.

152. The method of claim any one of claims 133-147, wherein the cell culture production medium comprises

a) a modified basal medium excluding the following components sodium bicarbonate, buffer, mono-basic sodium phosphate, di-basic sodium phosphate, an osmolarity regulator, a surfactant, and monosaccharide glucose;
b) about 8 to 12 ml/kg or 110 to 130 mg/L ferric citrate;
c) about 5 to 8 mL/kg or 11 to 15 mg/kg recombinant human insulin;
d) about 5 to 9 g/kg anhydrous glucose;
e) about 0.1 to 1 g/kg L-glutamine;
f) about 1 to 2 g/kg sodium bicarbonate
g) about 1 to 2 g/kg HEPES;
h) about 2 to 3 g/kg NaCl;
i) about 0.1 to 2 g/kg Pluronic F-68;
j) about 0.01 to 0.1 g/kg NaH_2PO_4-H_2O;
k) about 0.1 to 1 g/kg Na_2HPO_4-$7H_2O$;
l) about 6 to 12 g/kg yeast-based hydrolysate; and
m) about 6 to 8 g/kg plant-based hydrolysate.

153. The method of claim 152, wherein the cell culture production medium comprises

a) about 10 ml/kg or 122.45 mg/L ferric citrate;
b) about 6.5 mL/kg or 13 mg/kg recombinant human insulin;
c) about 7.0 g/kg anhydrous glucose;
d) about 0.58 to 0.59 g/kg L-glutamine;
e) about 1.6 g/kg sodium bicarbonate

f) about 1.8 g/kg HEPES;

g) about 2.45 g/kg NaCl;

h) about 1.0 g/kg Pluronic F-68;

i) about 0.03 to 0.04 g/kg NaH_2PO_4-H_2O;

j) about 0.43 to 0.44 g/kg Na_2HPO_4-$7H_2O$;

k) about 10.7 g/kg yeast-based hydrolysate; and

l) about 6.9 to 7.0 g/kg plant-based hydrolysate.

154. The method of any one of claims 133-153, wherein the cell culture is a large scale cell culture.

155. The method of claim 154, wherein the large scale cell culture is greater than 10 L.

156. The method of claim 154, wherein the large scale cell culture is about 13 L.

157. The method of any one of claims 133-156, wherein the anti-IL12 antibody is a fully human, anti-IL-12 antibody.

158. The method of claim 157, wherein the fully human, anti-IL-12 antibody is ABT-874.

159. A combination feed solution comprising

a) glucose;

b) a basal medium;

c) an amino acid other than glutamine; and

d) at least two different non-animal based hydrolysates;

wherein the feed solution has a pH of about 6.0 to 8.0.

160. The combination feed solution of claim 159, comprising about 100 to 250 g/kg glucose.

161. The combination feed solution of claim 159, wherein the amino acid is asparagine.

162. The combination feed solution of claim 160, comprising about 1.0 to 15.0 g of asparagine.

163. The combination feed solution of claim 161, comprising about 3.0 to 5.0 g/kg asparagine.

164. The combination feed solution of claim 159, wherein in the at least two different non-animal based hydrosylates are a plant-based hydrolysate and a hydrolysate which is not animal-based or plant based.

165. The combination feed solution of claim 164, wherein the hydrolysate which is not animal-based or plant-based is a yeast-based hydrolysate.

166. The combination feed solution of claim 164, wherein the plant-based hydrolysate is a soy-based hydrolysate.

167. The combination feed solution of claim 159, wherein the basal medium is either PF-CHO or DMEM/F12 medium.

168. The combination feed solution of claim 159, wherein the basal cell medium is a modified basal medium and excludes the following components: sodium bicarbonate, buffer, mono-basic sodium phosphate, di-basic sodium phosphate, an osmolarity regulator, a surfactant, glutamine, and glucose

169. The combination feed solution of any one of claims 159-168, further having a turbidity of less than about 15 NTU.

170. A method of maintaining a steady glucose level of a cell culture production medium comprising adding the combination feed solution of any one of claims 159-168.

171. A method for making a combination feed solution comprising a basal medium, glucose, and at least two different non-animal based hydrolysates comprising

a) combining glucose and the basal cell medium into a solution;

b) adjusting the pH of the solution of a) to about 9.5 to 10.5;

c) adding the at least two different non-animal based hydrolysates to the solution of b); and

d) adjusting the pH of the solution of c) such that the combination feed solution has a pH of about 6.5 to 7.5

172. The method of claim 171, wherein step c) comprises adding a first hydrolysate which is not animal-based or plant-based and a second plant-based hydrolysate.

173. The method of claim 172, wherein the hydrolysate which is not animal-based or plant-based is a yeast-based hydrolysate.

174. The method of claim 172, wherein the plant-based hydrolysate is a soy-based hydrolysate.

175. A method for producing at least about 1.5 g/L of an antibody from a mammalian cell culture comprising

a) culturing mammalian cells comprising a nucleic acid encoding the antibody in a cell culture production medium; and

b) adding a combination feed solution having a pH of about 6.7 to 7.2 to the cell culture production medium, wherein the combination feed solution comprises glucose; a basal cell medium; an amino acid other than glutamine; and at least two different non-animal based hydrosylates,

such that at least about 1.5 g/L of the antibody is produced.

176. The method of claim 175, wherein the combination feed solution comprises about 100 to 250 g/kg glucose.

177. The method of claim 175 wherein at least 2 g/L of the antibody is produced.

178. The method of claim 175, wherein at least 4 g/L of the antibody is produced.

179. The method of claim 175, wherein at least 5 g/L of the antibody is produced.

180. The method of claim 175, wherein about 6 g/L of the antibody is produced.

181. A method for increasing titer of an antibody produced from a mammalian cell culture comprising

a) culturing mammalian cells comprising a nucleic acid encoding the antibody in a cell culture production medium; and

b) adding a combination feed solution having a pH of about 6.7 to 7.2 to the cell culture production medium, wherein the combination feed solution comprises

glucose; a basal cell medium; an amino acid other than glutamine; and at least two different non-animal based hydrolysates,

such that the titer of the antibody produced is at least 50% more than a control mammalian cell culture which is cultured according to steps a) and and excluding step b).

182. The method of claim 181, wherein the titer of the antibody produced is at least 100% more than the control.

183. The method of claim 181, wherein the titer of the antibody produced is at least 150% more than the control.

184. The method of any one of claims 175-183, wherein the combination feed solution is added when the cell density reaches at least 2.0×10^6 cells / mL.

185. The method of any one of claims 175-183, wherein the combination feed solution is added when the cell density reaches about 3.5×10^6 cells / ml.

186. A method for producing a protein in a mammalian cell culture comprising

a) culturing mammalian cells comprising a nucleic acid encoding the protein in a cell culture production medium; and

b) adding a combination feed solution to the cell culture production medium using a feedback control system to monitor a metabolic indicator level in the cell culture production medium, wherein the combination feed solution is added to the cell culture production medium at a time point determined by the feedback control system,

such that the antibody is produced.

187. The method of claim 186, wherein the mammalian cell is a Chinese Hamster Ovary (CHO) cell.

188. The method of claim 186 or 187, wherein the metabolic indicator is glucose or glutamine.

189. The method of claim 186 or 187, wherein the feed solution is a combination feed solution comprising glucose; a basal cell medium; an amino acid other than glutamine; and at least two different non-animal based hydrolysates.

190. The method of claim 186 or 187, wherein the protein is an antibody.

191. The method of claim 190, wherein the antibody is selected from the group consisting of an anti-TNFα antibody, an anti-IL-12 antibody, an anti-IL-18 antibody, and an anti-EPO receptor (EPO-R) antibody.

192. The method of claim 190 or 191, wherein the antibody is produced at a titer of at least 1.5 g/L.

193. The method of claim 190 or 191, wherein the antibody is produced at a titer of at least 2 g/L.

194. The method of any one of claims 175-185 and 189, wherein the combination feed solution comprises about 3.0 to 12.5 g/kg asparagine.

195. The method of any one of claims 175-185 and 189, wherein the at least two different non-animal based hydrolysates comprise a plant-based hydrolysate and a hydrolysate which is not animal-based or plant-based.

196. The method of claim 195, wherein the hydrolysate which is not animal-based or plant-based is a yeast-based hydrolysate.

197. The method of claim 195, wherein the plant-based hydrolysate is a soy-based hydrolysate.

198. The method of any one of claims 175-185 and 189, wherein the combination feed solution comprises about 100 to 200 g/kg glucose.

199. The method of any one of claims 175-185 and 189, further comprising monitoring a glucose level in the cell culture medium such that the glucose level is maintained between about 0.25 and 20.0 g/L.

200. The method of claim 199, wherein the glucose level is monitored using an automated sampling device.

201. The method of any one of claims 175-185, wherein the antibody which is produced is selected from the group consisting of an anti-TNFα antibody, an anti-IL-18 antibody, and an anti-Il-12 antibody.

202. The method of claim 191 or 201, wherein the anti-TNFα antibody is D2E7 (adalimumab).

203. The method of claim 191 or 201, wherein the anti-IL-18 antibody is ABT-325.

204. The method of claim 191 or 201, wherein the anti-IL-12 antibody is ABT-874.

205. A method of determining a feed profile for producing a protein in a mammalian cell culture comprising

a) culturing mammalian cells comprising a nucleic acid encoding the antibody in a cell culture production medium; and

b) adding a combination feed solution to the cell culture production medium using a feedback control system to monitor a metabolic indicator in the cell culture production medium, wherein the combination feed solution is added to the cell culture production medium to meet a target metabolic indicator setpoint; and

c) determining the amount of the combination feed solution added to the cell culture production medium per day,

such that a feed profile is determined.

206. The method of claim 205, wherein the metabolic indicator is glucose or glutamine.

207. A fed batch method for producing a protein in a mammalian cell culture comprising adding a combination feed solution to the mammalian cell culture according to the feed profile of claim 205.

208. A method of producing an antibody in a mammalian cell culture such that the titer of the antibody is at least 100 mg/L, said method comprising

a) culturing mammalian cells comprising a nucleic acid encoding the antibody in a cell culture production medium;

b) adding sodium butyrate, N-acetylcysteine, or a combination thereof, to the cell culture medium, wherein the sodium butyrate is added to a final concentration of about 0.1 mM to 10 mM and the N-acetylcysteine is added to a final concentration of about 1 mM to 80 mM ,

such that the antibody is produced at a titer of at least 100 mg/L.

209. The method of claim 208, wherein the antibody titer is at least 150 mg/L.

210. The method of claim 208, wherein the antibody titer is at least 200 mg/L.

211. The method of claim 208, wherein the antibody titer is at least 250 mg/L.

212. The method of claim 208, wherein the antibody titer is at least 300 mg/L.

213. The method of claim 208, wherein the antibody titer is at least 400 mg/L.

214. A method of producing an antibody in a mammalian cell culture such that the titer of the antibody is at least 10% greater than a control mammalian cell culture, said method comprising

a) culturing mammalian cells comprising a nucleic acid encoding the antibody in a cell culture production medium; and

b) adding sodium butyrate, N-acetylcysteine, or a combination thereof, to the cell culture medium, wherein the sodium butyrate is added to a final concentration of about 0.1 mM to 10 mM and the N-acetylcysteine is added to a final concentration of about 1 mM to 80 mM,

such that the titer of the antibody is at least 10% greater than the control, wherein the control mammalian cell culture comprises step a) and excludes step b).

215. The method of claim 214, wherein the antibody titer of the mammalian cell culture is improved at least 29% over the control mammalian cell culture.

216. The method of claim 214, wherein the antibody titer of the mammalian cell culture is improved at least 40% over the control mammalian cell culture.

217. The method of claim 214, wherein the antibody titer of the mammalian cell culture is improved at least 70% over the control mammalian cell culture.

218. The method of claim 214, wherein the antibody titer of the mammalian cell culture is at least 90% greater than the control mammalian cell culture.

219. The method of any one of claims 208-218, wherein sodium butyrate, N-acetylcysteine, or combination thereof, is added to the mammalian cell culture during the

growth phase of the mammalian cell culture.

220. The method of any one of claims 208-218, wherein the sodium butyrate, N-acetylcysteine, or combination thereof is added to the mammalian cell culture between days 4 and 7 of the culture time.

221. The method of any one of claims 208-218, wherein the sodium butyrate, N-acetylcysteine, or combination thereof is added to the mammalian cell culture on day 0 of the culture time.

222. The method of any one of claims 208-218, wherein the final concentration of sodium butyrate is about 0.1 mM to 10 mM.

223. The method of any one of claims 208-218, wherein the final concentration of sodium butyrate is about 0.1 mM to 8.0 mM.

224. The method of any one of claims 208-218, wherein the final concentration of sodium butyrate is about 0.1 mM to 3.0 mM of sodium butyrate.

225. The method of any one of claims 208-218, wherein the final concentration of N-acetylcysteine is about 20 mM to 60 mM.

226. The method of any one of claims 208-218, wherein the final concentration of N-acetylcysteine is about 10 mM.

227. The method of any one of claims 208-218, wherein the final concentration of N-acetylcysteine is about 8 mM.

228. A method of extending longevity of a mammalian cell culture by at least 35% in comparison to a control mammalian cell culture, said method comprising

a) culturing mammalian cells comprising a nucleic acid encoding the antibody in a cell culture production medium; and

b) adding about 1 mM to 80 mM N-acetylcysteine to the cell medium; a

such that the longevity of the mammalian cell culture is extended by at least 35% in comparison to a control mammalian cell culture, wherein the control mammalian cell culture comprises step a) and excludes step b).

229. The method of claim 228, wherein the longevity of the mammalian cell culture is extended at least about 45 % in comparison to the control mammalian cell culture.

230. The method of claim 228, wherein the longevity of the mammalian cell culture is extended at least about 55 % in comparison to the control mammalian cell culture.

231. The method of any one of claims 228-230, comprising adding a final concentration of about 8 mM N-acetylcysteine to the cell culture production medium.

232. The method of any one of claims 208-231, wherein the antibody is selected from the group consisting of an anti-TNFα antibody, an anti-IL-18 antibody, and an anti-Il-12 antibody.

233. The method of claim 232, wherein the anti-IL-18 antibody is ABT-325.

What is claimed:

1. A method of producing an anti-TNFα antibody in a mammalian cell culture, said method comprising:

a) culturing Chinese Hamster Ovary (CHO) cells comprising a nucleic acid encoding the antibody, or a fragment thereof, in a cell culture growth medium to form the mammalian cell culture; and

b) culturing the CHO cells in a cell culture production medium, wherein glucose is added to the mammalian cell culture to maintain a glucose concentration of at least 2 g/L,

such that the anti-TNFα antibody is produced,

wherein the anti-TNFα antibody comprises a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO:5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO:8.

2. The method of claim 1, wherein the CHO cells are cultured in a cell culture growth medium at a temperature ranging from 32° to 38° C.

3. The method of claim 1, wherein the CHO cells are cultured in a cell production medium at a temperature ranging from 32° to 38° C.

4. The method of claim 1, wherein the CHO cells are cultured in a cell growth phase at a temperature of about 35° C.

5. The method of claim 1, wherein the cell culture growth media comprises methotrexate.

6. The method of claim 1, wherein the cell culture production media comprises methotrexate.

7. The method of claim 1, wherein the cell culture growth media comprises at least one hydrolysate.

8. The method of claim 1, wherein the cell culture production media comprises at least one hydrolysate.

9. The method of claim 1, wherein the culturing of the CHO cells is performed in a large-scale cell culture.

10. The method of claim 1, wherein the mammalian cell culture further comprises a cell protectant.

11. The method of claim 1, wherein the glucose concentration is maintained from 2 g/L to 5 g/L.

12. A method of producing an anti-TNFα antibody in a mammalian cell culture, said method comprising:

a) culturing Chinese Hamster Ovary (CHO) cells comprising a nucleic acid encoding the antibody, or a fragment thereof, in a cell culture growth medium to form the mammalian cell culture; and

b) culturing the CHO cells in a cell culture production medium, wherein glucose is added to the mammalian cell culture to maintain a glucose concentration of at least 2 g/L,

such that the anti-TNFα antibody is produced,

wherein the anti-TNFα antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:1, and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:2.

13. The method of claim 12, wherein the CHO cells are cultured in a cell culture growth medium at a temperature ranging from 32° C. to 38° C.

14. The method of claim 12, wherein the CHO cells are cultured in a cell production medium at a temperature ranging from 32° to 38° C.

15. The method of claim 12, wherein the CHO cells are cultured in a cell growth phase at a temperature of about 35°C.

16. The method of claim 12, wherein the cell culture growth media comprises methotrexate.

17. The method of claim 12, wherein the cell culture production media comprises methotrexate.

18. The method of claim 12, wherein the cell culture growth media comprises at least one hydrolysate.

19. The method of claim 12, wherein the cell culture production media comprises at least one hydrolysate.

20. The method of claim 12, wherein the culturing of the CHO cells is performed in a large-scale cell culture.

21. The method of claim 12, wherein the mammalian cell culture further comprises a cell protectant.

22. The method of claim 12, wherein the glucose concentration is maintained from 2 g/L to 5 g/L.

23. A method of producing adalimumab in a mammalian cell culture, said method comprising:

a) culturing Chinese Hamster Ovary (CHO) cells comprising a nucleic acid encoding adalimumab, or a fragment thereof, in a cell culture growth medium to form the mammalian cell culture; and

b) culturing the CHO cells in a cell culture production medium, wherein glucose is added to the mammalian cell culture to maintain a glucose concentration of at least 2 g/L,

such that adalimumab is produced.

24. The method of claim 23, wherein the CHO cells are cultured in a cell culture growth medium at a temperature ranging from 32° C. to 38° C.

25. The method of claim 23, wherein the CHO cells are cultured in a cell production medium at a temperature ranging from 32° to 38° C.

26. The method of claim 23, wherein the cell growth phase is at a temperature of about 35° C.

27. The method of claim 23, wherein the cell culture growth media comprises methotrexate.

28. The method of claim 23, wherein the cell culture production media comprises methotrexate.

29. The method of claim 23, wherein the cell culture growth media comprises at least one hydrolysate.

30. The method of claim 23, wherein the cell culture production media comprises at least one hydrolysate.

31. The method of claim 23, wherein the culturing of the CHO cells is performed in a large-scale cell culture.

32. The method of claim 23, wherein the mammalian cell culture further comprises a cell protectant.

33. The method of claim 23, wherein the glucose concentration is maintained from 2 g/L to 5 g/L.

34. A method of producing an anti-TNFα antibody, or an antigen-binding fragment thereof, in a mammalian cell culture, said method comprising culturing Chinese Hamster Ovary (CHO) cells expressing the anti-TNFα antibody, or the antigen-binding fragment thereof, in a cell culture production medium, wherein glucose is added to the cell culture production medium to maintain a glucose concentration of at least 2 g/L, such that the anti-TNFα antibody, or the antigen-binding fragment thereof, is produced,

wherein the anti-TNFα antibody, or the antigen-binding fragment thereof, comprises a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8.

35. The method of claim 34, wherein the glucose concentration is maintained from 2 g/L to 5 g/L.

36. The method of claim 34, wherein the anti-TNFα antibody, or antigen-binding fragment thereof, comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:1, and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:2.

37. The method of claim 36, wherein the glucose concentration is maintained from 2 g/L to 5 g/L.

38. The method of claim 34, wherein the anti-TNFα antibody is adalimumab, or an antigen-binding fragment thereof.

39. The method of claim 38, wherein the glucose concentration is maintained from 2 g/L to 5 g/L.