CLAIMS

1. A method for culturing recombinant eukaryotic cells for improved recombinant protein production, comprising the steps of: (a) propagating or maintaining cells in a defined cell culture medium during growth phase, and (b) supplementing the base cell culture medium with 0.1 mM to 10 mM L-taurine and 0.09 mM to 0.9 mM ornithine and expressing a recombinant protein of interest during production phase, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

2. The method of claims 1, 28, or 29 wherein the supplements of (b) are provided from 1 to 5 times during production phase.

3. The method of claims 1, 28, or 29 wherein the supplements of (b) are provided on each day for the duration of the production phase.

4. The method of claims 1, 28, or 29 further comprising supplementing the culture in a defined cell culture medium with 0.1 mM to 10 mM L-taurine during growth phase.

5. The method of claims 1, 28, or 29 wherein the eukaryotic cell is selected from the group consisting of mammalian cell, avian cell, insect cell, and yeast cell.

6. The method of claim 5, wherein the cell is selected from the group consisting of CHO (e.g. CHO K1, DXB-11 CHO, Veggie-CHO), COS (e.g. COS-7), retinal cell, Vero, CV1, kidney (e.g. HEK293, 293 EBNA, MSR 293, MDCK, HaK, BHK21), HeLa, HepG2, WI38, MRC 5, Colo25, HB 8065, HL-60, lymphocyte (e.g. Jurkat, Daudi), A431 (epidermal), CV-1, U937, 3T3, L cell, C127 cell, SP2/0, NS-0, MMT cell, PER.C6® cell, stem cell, tumor cell, and a cell line derived from an aforementioned cell.

7. The method of claim 6, wherein the cell is a CHO cell.

8. The method of claims 1, 28, or 29 wherein the protein of interest is an antigen binding protein.

9. The method of claims 1, 28, or 29 wherein the protein of interest comprises an Fc domain.

10. The method of claim 8, wherein the protein of interest is selected from the group consisting of an Fc-fusion protein, a receptor-Fc-fusion protein (TRAP), an antibody, an antibody fragment, and a ScFv-Fc fusion protein.

11. The method of claim 10, wherein the protein of interest is selected from the group consisting of an anti-PD1 antibody, an anti-PDL-1 antibody, an anti-Dll4 antibody, an anti-ANG2 antibody, an anti-AngPtl3 antibody, an anti-PDGFR antibody, an anti-Erb3 antibody, an anti-PRLR antibody, an anti-TNF antibody, an anti-EGFR antibody, an anti-PCSK9 antibody, an anti-GDF8 antibody, an anti-GCGR antibody, an anti-VEGF antibody, an anti-IL1R antibody, an anti-IL4R antibody, an anti-IL6R antibody, an anti-IL1 antibody, an anti-IL2 antibody, an anti-IL3 antibody, an anti-IL4 antibody, an anti-IL5 antibody, an anti-IL6 antibody, an anti-IL7 antibody, an anti-RSV antibody, an anti-NGF antibody, an anti-CD3 antibody, an anti-CD20 antibody, an anti-CD19 antibody, an anti-CD28 antibody, an anti-CD48 antibody, an anti-CD3/anti-CD20 bispecific antibody, an anti-CD3/anti-MUC16 bispecific antibody, and an anti-CD3/anti-PSMA bispecific antibody.

12. The method of claim 10, wherein the protein of interest is selected from the group consisting of alirocumab, sarilumab, fasinumab, nesvacumab, dupilumab, trevogrumab, evinacumab, and rinucumab.

13. A method for producing a recombinant protein of interest comprising the steps of:

(a) introducing into a cell or cells a nucleic acid comprising a nucleotide sequence encoding a protein of interest;

(b) selecting the cell(s) expressing the protein of interest;

(c) culturing the selected cell(s) in a cell culture medium comprising 0.1 mM to 10 mM L-taurine and 0.09 mM to 0.9 mM ornithine; and

(d) producing the protein of interest in the cell, wherein the protein of interest is secreted into the medium, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

14. The method of claims 13, 30, or 31 wherein the cell is a CHO cell, HEK293 cell or BHK cell.

15. The method of claims 13, 30, or 31 wherein the protein of interest is an antigen-binding protein.

16. The method of claims 13, 30, or 31 wherein the protein of interest comprises an Fc domain.

17. The method of claims 13, 30, or 31 wherein the protein of interest is selected from the group consisting of an Fc-fusion protein, a receptor-Fc-fusion protein (TRAP), an antibody, and an antibody fragment.

18 The method of claim 17, wherein the protein of interest is selected from the group consisting of an anti-PD1 antibody, an anti-PDL-1 antibody, an anti-Dll4 antibody, an anti-ANG2 antibody, an anti-AngPtl3 antibody, an anti-PDGFR antibody, an anti-Erb3 antibody, an anti-PRLR antibody, an anti-TNF antibody, an anti-EGFR antibody, an anti-PCSK9 antibody, an anti-GDF8 antibody, an anti-GCGR antibody, an anti-VEGF antibody, an anti-IL1R antibody, an anti-IL4R antibody, an anti-IL6R antibody, an anti-IL1 antibody, an anti-IL2 antibody, an anti-IL3 antibody, an anti-IL4 antibody, an anti-IL5 antibody, an anti-IL6 antibody, an anti-IL7 antibody, an anti-RSV antibody, an anti-NGF antibody, an anti-CD3 antibody, an anti-CD20 antibody, an anti-CD19 antibody, an anti-CD28 antibody, an anti-CD48 antibody, an anti-CD3/anti-CD20 bispecific antibody, an anti-CD3/anti-MUC16 bispecific antibody, and an anti-CD3/anti-PSMA bispecific antibody.

19. The method of claim 17, wherein the protein of interest is selected from the group consisting of alirocumab, sarilumab, fasinumab, nesvacumab, dupilumab, trevogrumab, evinacumab, and rinucumab.

20. A method for producing a protein of interest in a taurine-supplemented culture medium, comprising the steps of:

(a) introducing into a cell a nucleic acid comprising a sequence encoding a protein of interest;

(b) selecting a cell or cells expressing the protein of interest;

(c) culturing the selected cell(s) in a cell culture medium;

(d) supplementing the cell culture medium with taurine in an amount of 0.1 mM to 10 mM and ornithine in an amount of 0.09 mM to 0.9 mM;

(e) maintaining the cell culture under taurine supplementation conditions of (d) for at least 6 days, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine, wherein the protein of interest is secreted into the medium; and

(f) harvesting the protein of interest.

21. The method of claims 20, 32, or 33 wherein the harvested protein has a protein titer that is at least 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or at least 20% higher than the titer of a comparator control culture wherein the comparator control culture medium has not been subjected to the taurine supplementation conditions of (d).

22. A method for producing at least 1 g/L of a recombinant protein of interest comprising culturing a recombinant cell line in a cell culture medium comprising at least 0.1 mM L-taurine and at least 0.09 mM ornithine, wherein the cell line comprises a stably integrated nucleic acid encoding the recombinant protein, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

23. The method of claims 22, 34, or 35 wherein yield of the recombinant protein of interest was increased by the inclusion of taurine in the medium compared to a cell line cultured in a cell culture medium that does not include L-taurine.

24. The method of claims 22, 34, or 35 wherein the protein of interest is selected from the group consisting of an Fc-fusion protein, a receptor-Fc-fusion protein (TRAP), an antibody, and an antibody fragment.

25. The method of claim 24, wherein the protein of interest is selected from the group consisting of an anti-PD1 antibody, an anti-PDL-1 antibody, an anti-Dll4 antibody, an anti-ANG2 antibody, an anti-AngPtl3 antibody, an anti-PDGFR antibody, an anti-Erb3 antibody, an anti-PRLR antibody, an anti-TNF antibody, an anti-EGFR antibody, an anti-PCSK9 antibody, an anti-GDF8 antibody, an anti-GCGR antibody, an anti-VEGF antibody, an anti-IL1R antibody, an anti-IL4R antibody, an anti-IL6R antibody, an anti-IL1 antibody, an anti-IL2 antibody, an anti-IL3 antibody, an anti-IL4 antibody, an anti-IL5 antibody, an anti-IL6 antibody, an anti-IL7 antibody, an anti-RSV antibody, an anti-NGF antibody, an anti-CD3 antibody, an anti-CD20 antibody, an anti-CD19 antibody, an anti-CD28 antibody, an anti-CD48 antibody, an anti-CD3/anti-CD20 bispecific antibody, an anti-CD3/anti-MUC16 bispecific antibody, and an anti-CD3/anti-PSMA bispecific antibody.

26. The method of claim 24, wherein the protein of interest is selected from the group consisting of alirocumab, sarilumab, fasinumab, nesvacumab, dupilumab, trevogrumab, evinacumab, and rinucumab.

27. The method of claim 24, wherein the production method is capable of increasing protein yield by at least 0.1 g/L, at least 0.5 g/L, at least 1 g/L, at least 1.2 g/L, at least 1.4 g/L, at least 1.6 g/L, at least 1.8 g/L, at least 2 g/L, at least 2.2 g/L, at least 2.4 g/L, or at least 2.5 g/L compared to a similar production method in a cell culture medium that contains less than 0.1 mM taurine.

28. A method for culturing recombinant eukaryotic cells for improved recombinant protein production, comprising the steps of: (a) propagating or maintaining cells in a defined cell culture medium during growth phase, and (b) supplementing the base cell culture medium with 0.1 mM to 10 mM L-taurine and 0.20 mM to 0.714 mM putrescine and expressing a recombinant protein of interest during production phase, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

29. A method for culturing recombinant eukaryotic cells for improved recombinant protein production, comprising the steps of: (a) propagating or maintaining cells in a defined cell culture medium during growth phase, and (b) supplementing the base cell culture medium with ~~about~~ 0.1 mM to 10 mM L-taurine, 0.09 mM to 0.9 mM ornithine, and 0.20 mM to 0.714 mM putrescine and expressing a recombinant protein of interest during production phase, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

30. A method for producing a recombinant protein of interest comprising the steps of:

(a) introducing into a cell or cells a nucleic acid comprising a nucleotide sequence encoding a protein of interest;

(b) selecting the cell(s) expressing the protein of interest;

(c) culturing the selected cell(s) in a cell culture medium comprising 0.1 mM to 10 mM L-taurine and 0.20 mM to 0.714 mM putrescine; and

(d) producing the protein of interest in the cell, wherein the protein of interest is secreted into the medium, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

31. A method for producing a recombinant protein of interest comprising the steps of:

(a) introducing into a cell or cells a nucleic acid comprising a nucleotide sequence encoding a protein of interest;

(b) selecting the cell(s) expressing the protein of interest;

(c) culturing the selected cell(s) in a cell culture medium comprising 0.1 mM to 10 mM L-taurine, 0.09 mM to 0.9 mM ornithine, and 0.20 mM to 0.714 mM putrescine; and

(d) producing the protein of interest in the cell, wherein the protein of interest is secreted into the medium, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at

least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

32. A method for producing a protein of interest in a taurine-supplemented culture medium, comprising the steps of:

(a) introducing into a cell a nucleic acid comprising a sequence encoding a protein of interest;

(b) selecting a cell or cells expressing the protein of interest;

(c) culturing the selected cell(s) in a cell culture medium;

(d) supplementing the cell culture medium with taurine in an amount of 0.1 mM to 10 mM and putrescine in an amount of 0.20 mM to 0.714 mM;

(e) maintaining the cell culture under taurine supplementation conditions of (d) for at least 6 days, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine, wherein the protein of interest is secreted into the medium; and

(f) harvesting the protein of interest.

33. A method for producing a protein of interest in a taurine-supplemented culture medium, comprising the steps of:

(a) introducing into a cell a nucleic acid comprising a sequence encoding a protein of interest;

(b) selecting a cell or cells expressing the protein of interest;

(c) culturing the selected cell(s) in a cell culture medium;

(d) supplementing the cell culture medium with taurine in an amount of 0.1 mM to 10 mM, ornithine in an amount of 0.09 mM to 0.9 mM, and putrescine in an amount of 0.20 mM to 0.714 mM;

(e) maintaining the cell culture under taurine supplementation conditions of (d) for at least 6 days, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine, wherein the protein of interest is secreted into the medium; and

(f) harvesting the protein of interest.

34. A method for producing at least 1 g/L of a recombinant protein of interest comprising culturing a recombinant cell line in a cell culture medium comprising at least 0.1 mM L-taurine and at least 0.20 mM putrescine, wherein the cell line comprises a stably integrated nucleic acid encoding the recombinant protein, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

35. A method for producing at least 1 g/L of a recombinant protein of interest comprising culturing a recombinant cell line in a cell culture medium comprising at least 0.1 mM L-taurine, at least 0.09 mM ornithine, and at least 0.20 mM putrescine, wherein the cell line comprises a stably integrated nucleic acid encoding the recombinant protein, wherein the addition of L-taurine increases the titer of the recombinant protein of interest by at least 3% when compared to cells expressing the protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

36. The method of claims 1, 28 or 29, wherein the addition of L-taurine reduces the ammonia byproduct level by at least 4% compared to cells expressing the recombinant protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

37. The method of claims 13, 30 or 31, wherein the addition of L-taurine reduces the ammonia byproduct level by at least 4% compared to cells expressing the recombinant protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

38. The method of claims 22, 34, or 35, wherein the addition of L-taurine reduces the ammonia byproduct level by at least 4% compared to cells expressing the recombinant protein of interest in a cell culture medium containing less than 0.1 mM L-taurine.

39. The method of claims 1, 28 or 29, wherein the titer of the recombinant protein of interest cultured in the media containing 0.1 mM to 10 mM L-taurine supplement is at least 1.8 g/L.

40. The method of claims 13, 30 or 31, wherein the titer of the recombinant protein of interest cultured in the media containing 0.1 mM to 10 mM L-taurine supplement is at least 1.8 g/L.

41. The method of claims 22, 34, or 35, wherein the titer of the recombinant protein of interest cultured in the media containing 0.1 mM to 10 mM L-taurine supplement is at least 1.8 g/L.