about 0.05 μM to about 0.5 μM hydrocortisone; from about 0.11 μM to about 0.72 μM vitamin B2; from about 4.5 μM to about 30.0 μM vitamin B6; from about 3.4 μM to about 22.0 μM vitamin B9; and from about 0.2 μM to about 1.5 μM vitamin B12, and where the cell culture medium may further comprise one or more of the following components: (1) vitamin B1 (which in one embodiment is present at a concentration from about 2.0 μM to about 14.0 μM), (2) vitamin B3 (which in one embodiment is present at a concentration from about 11.0 μM to about 72.0 μM), (3) vitamin B5 (which in one embodiment is present at a concentration from about 6.8 μM to about 44.0 μM), and (4) vitamin B7 (which in one embodiment is present at a concentration from about 0.02 μM to about 0.24 μM).

[0018] Methods of producing a polypeptide by growing in a cell culture medium (*i.e.*, culturing in a cell culture medium) a cell comprising an isolated nucleic acid encoding the polypeptide are also provided, wherein: (a) the cell expresses the polypeptide and (b) the cell culture medium comprises: (1) from about 300 mg/L (in some embodiments, 200 mg/L) to about 1200 mg/L cystine; (2) from about 0.05 mg/L to about 1.0 mg/L vitamin B2; (3) from about 0.05 mg/L to about 10.0 mg/L vitamin B6; (4) from about 0.05 mg/L to about 12.0 mg/L vitamin B9; and (5) from about 0.05 mg/L to about 2.5 mg/L vitamin B12, and where the cell culture medium may further comprise one or more of the following components: (A) an iron source, such as ferric citrate or ferrous sulfate (which in one embodiment is present at a concentration of from about 2 μM to about 80 μM) and (B) hydrocortisone (which in one embodiment is present at a concentration from about 0.05 μM to about 0.25 μM).

[0018a] In one aspect, there is provided a method of producing an antibody comprising the steps of (a) culturing in a basal cell culture medium a cell comprising an isolated nucleic acid encoding the antibody, wherein:

the basal cell culture medium comprises:

from 200 mg/L to 1200 mg/L cystine;

from 0.05 mg/L to 1.0 mg/L vitamin B2;

from 0.05 mg/L to 10.0 mg/L vitamin B6;

from 0.05 mg/L to 12.0 mg/L vitamin B9;

from 0.05 mg/L to 2.5 mg/L vitamin B12; and

from 2 μM to 80 μM ferric citrate and the cell expresses the antibody; and

(b) purifying the antibody expressed by the cell, wherein if the purified antibody is concentrated to a concentration of 100 mg/mL to 150 mg/mL, then the purified antibody has a

CLAIMS

What is claimed is:

1. A method of producing an antibody comprising the steps of

(a) culturing in a basal cell culture medium a cell comprising an isolated nucleic acid encoding the antibody, wherein:

the basal cell culture medium comprises:

from 200 mg/L to 1200 mg/L cystine;

from 0.05 mg/L to 1.0 mg/L vitamin B2;

from 0.05 mg/L to 10.0 mg/L vitamin B6;

from 0.05 mg/L to 12.0 mg/L vitamin B9;

from 0.05 mg/L to 2.5 mg/L vitamin B12; and

from 2 μM to 80 μM ferric citrate and

the cell expresses the antibody; and

(b) purifying the antibody expressed by the cell, wherein if the purified antibody is concentrated to a concentration of 100 mg/mL to 150 mg/mL, then the purified antibody has a color that is lighter than a reference standard color value selected from the group consisting of B1, BY1, Y1, GY1, and R1 according to the European Pharmacopeia color standards.

2. The method of claim 1, wherein the basal cell culture medium comprises:
from 0.7 mM to 2.5 mM cystine;
from 0.11 μM to 0.72 μM vitamin B2;
from 4.5 μM to 30.0 μM vitamin B6;
from 3.4 μM to 22.0 μM vitamin B9; and
from 0.2 μM to 1.5 μM vitamin B12.

3. The method of claim 1 or 2, wherein the basal cell culture medium further comprises any one or more of vitamin B1, vitamin B3, vitamin B5 and vitamin B7.

4. The method of claim 3, wherein the basal cell culture medium further comprises any one or more of:
from 2.0 μM to 14.0 μM vitamin B1;
from 11.0 μM to 72.0 μM vitamin B3;
from 6.8 μM to 44.0 μM vitamin B5; and
from 0.02 μM to 0.14 μM vitamin B7.

5. The method of any one of claims 1-4, wherein the basal cell culture medium comprises ferric citrate at a concentration of from 11.0 μM to 36.0 μM.

6. The method of any one of claims 1-5, wherein the basal cell culture medium further comprises hydrocortisone.

7. The method of claim 6, wherein the concentration of hydrocortisone in the basal cell culture medium is from 0.05 μM to 0.25 μM.

8. The method of any one of claims 1-7, wherein the basal cell culture medium is a chemically defined cell culture medium.

9. The method of any one of claims 1-7, wherein the basal cell culture medium is a chemically undefined cell culture medium.

10. The method of any one of claims 1-9, wherein the culturing is during the cell's growth phase.

11. The method of any one of claims 1-10, wherein the culturing is during the cell's production phase.

12. The method of claim 11, wherein the method further comprises a step of adding cysteine to the basal cell culture medium.

13. The method of claim 12, wherein the cysteine is added in an amount to provide from 80 mg/L to 1500 mg/L cysteine in the basal cell culture medium.

14. The method of claim 12, wherein the cysteine is added in an amount to provide 1500 mg/L cysteine in the basal cell culture medium.

15. The method of claim 12, wherein the cysteine is added in an amount to provide 140 mg/L cysteine in the basal cell culture medium.

16. The method of any one of claims 1-15, wherein the antibody is an IgG1 antibody.

17. The method of any one of claims 1-15, wherein the antibody is an anti-VEGF, anti-mesothelin, anti-PCSK9 or anti-Beta7 antibody.

18. The method of any one of claims 1-15, wherein if the purified antibody is concentrated to a concentration of 125 mg/mL, then the purified antibody has a color that is lighter than a reference standard color value selected from the group consisting of B1, BY1, Y1, GY1, and R1 according to the European Pharmacopeia color standards.

19. The method of any one of claims 1-15, wherein if the purified antibody is concentrated to a concentration of 150 mg/mL, then the purified antibody has a color that is lighter than a reference standard color value selected from the group consisting of B1, BY1, Y1, GY1, and R1 according to the European Pharmacopeia color standards.

20. The method of any one of claims 1-15, wherein if the purified antibody is concentrated to a concentration of 100 mg/mL to 150 mg/mL, then the purified antibody has a color that is lighter than a reference standard color value selected from the group consisting of B2, BY2, Y2, GY2, and R2 according to the European Pharmacopeia color standards.

21. The method of any one of claims 1-15, wherein if the purified antibody is concentrated to a concentration of 100 mg/mL to 150 mg/mL, then the purified antibody has a color that is lighter than a reference standard color value selected from the group consisting of B3, BY3, Y3, GY3, and R3 according to the European Pharmacopeia color standards.

22. The method of any one of claims 1-15, wherein the color of the purified antibody is determined by an assay selected from the group consisting of the COC assay, the Total Color assay, and the NIFTY assay.

23. The method of any one of claims 1-15, further comprising (c) concentrating the purified antibody in step (b) to a concentration of at least 100 mg/mL.

24. The method of claim 23, wherein the purified antibody is concentrated to a concentration of at least 125 mg/mL.

25. The method of claim 23, wherein the purified antibody is concentrated to a concentration of at least 150 mg/mL.

26. The method of any one of claims 1-15, further comprising culturing the cell in feed cell culture medium.

27. The method of claim 26, wherein the feed cell culture medium does not contain iron.

28. The method of claim 26, wherein the feed cell culture medium does not contain one or more of vitamin B2, B6, B9, and B12.

29. The method of claim 26, wherein the feed cell culture medium does not contain vitamin B2, B6, B9, and B12.