CLAIMS

1. A method of producing a stabilized product expressed in a recombinant host cell, comprising:

providing a redox potential difference in the range of -50m V to -300m V from a non-stabilized product to the stabilized product in a post-exponential growth culture phase of a production culture,

cooling the production culture at the end of a production phase to a $T_{harvest}$ temperature which is a temperature that is below the temperature at which the recombinant host cell was or is normally cultured; and

maintaining the redox potential difference during separation of the recombinant host cell from the production culture and collection of a supernatant,

thereby producing the stabilized product.

2. A method of producing a stabilized product expressed in a recombinant host cell, comprising:

providing a redox potential difference in the range of -50mV to -300mV from a non-stabilized product to the stabilized product in a post-exponential growth culture phase of a production culture, wherein dissolved oxygen tension (DOT) from a start of a production phase to an end of the production phase is in a range of greater than 40% air saturation;

cooling the production culture at the end of the production phase to a $T_{harvest}$ temperature, which is a temperature that is below the temperature at which the cell was or is normally cultured;

increasing the DOT to a range of greater than 40% to less than 500% air saturation by sparging air or O_2 gas into the production culture until separation of cells from the production culture and collection of supernatant; and

maintaining the redox potential difference during separation of the recombinant host cell cells from the production culture and collection of a supernatant,

thereby producing the stabilized product.

3. A method of producing a stabilized product, expressed in a recombinant host cell, comprising:

(i) providing a post-exponential growth culture, comprising a recombinant host cell expressing the product at a redox potential difference in the range of -50mV to -300mV from a non-stabilized product to a stabilized product;

(ii) maintaining the redox potential difference in a post-growth culture phase; and

(iii) maintaining the redox potential during separation of cells from production culture and collection of a supernatant,

wherein the method comprises:

a. cooling the production culture after exponential growth phase has occurred, to a temperature $T_{production}$ of 30°C to 33°C, which is a temperature that is below the temperature at which the recombinant host cell was or is normally cultured; and one or more of the following steps:

b. oxygenating the production culture, to a dissolved oxygen tension (DOT) greater than 40% to less than or equal to 70% air saturation from start of the production phase to the end of the production phase;

c. providing transition metals in or to the production culture, wherein the transition metals comprise Zn^{2+}, Mn^{4+}, Cu^{2+}, Fe^{3+}, Co^{2+}, Cr^{3+}, and/or Ni^{2+};

d. providing dehydroascorbic acid or ascorbic acid, or a dehydroascorbic acid or ascorbic acid modifying component, to the production culture;

e. providing glutathione, e.g., oxidized and/or reduced glutathione, or a glutathione modifying component, to the production culture; or

f. cooling the production culture for separation of cells from production culture and collection of supernatant to a temperature $T_{harvest}$ of 12°C-18°C, which is a temperature that is below $T_{production}$,

thereby producing a stabilized product.

4. The method of claim 3, wherein the method comprises steps a, b, and f.

5 The method of claim 3, wherein the method comprises steps a, c, and f.

6. The method of claim 3, wherein the method comprises steps a, b and c.

7. The method of claim 3, wherein the method comprises steps a, b, c, and f.

8. The method of claim 2, wherein $T_{harvest}$ is sufficiently low to inhibit dissociation of the disulfide bond.

9. The method of claim 2, comprising separating the recombinant host cell from the production culture at $T_{harvest}$.

10. The method of claim 2, wherein the recombinant host cell line is cultured at a first temperature, $T_{culture}$, and is harvested at $T_{harvest}$.

11. The method of claim 10, wherein $T_{harvest}$ is at least 19° to 25° C below $T_{culture}$.

12. The method of claim 2, wherein $T_{harvest}$ is 12°C to 18°C.

13. The method of claim 10, wherein $T_{culture}$ is 30°C to 38°C.

14. The method of claim 2, wherein the stabilized product is applied to a filter at $T_{harvest}$.

15. The method of claim 2, wherein the recombinant host cell is cultured in a bioreactor.

16. The method of claim 15, wherein the contents of the bioreactor are cooled to $T_{harvest}$ after production phase.

17. The method of claim 15, wherein the cell culture is cooled by contact with a member comprising a fluid at a temperature suitable for bringing the cell culture to $T_{harvest}$.

18. The method of claim 15, wherein the bioreactor has a volume of 50 liters to 800 liters.

19. The method of claim 15, wherein the bioreactor is a single use bioreactor.

20. The method of claim 15, wherein the bioreactor comprises a bioprocess container, a shell, at least one agitator, at least one sparger, at least one gas filter inlet port for the sparger(s) and headspace overlay, at least one fill port, at least one harvest port, at least one sample port, and at least one probe.

21. The method of claim 15, wherein the bioreactor comprises processes and probes for monitoring and maintaining one or more of pH, dissolved oxygen tension (DOT), or temperature.

22. The method of claim 15, wherein the bioreactor is a self-supporting biocompatible tank having a volume of at least 4000 L and at least one top impeller and at least one bottom

impeller, and wherein the at least one top impeller is a hydrofoil impeller, and wherein an impeller spacing (D_s) between the top impeller and the bottom impeller is at least 1.229x the diameter of the bottom impeller (D_{bottom}) and at most $2xD_{bottom}$, wherein a liquid height above the top impeller (D_o) is at least 0.3x the diameter of the top impeller (D_{top}) and at most $2.5xD_{top}$, and wherein a bottom clearance (D_c) between the tank bottom and the center-line of the bottom impeller is at least $0.35xD_{bottom}$.

23. The method of claim 15, wherein the bioreactor is operably coupled to a harvest vessel.

24. The method of claim 23, wherein the harvest vessel is configured to comprise or provide a head space above the reservoir culture, wherein the head space comprises a gas or a mixture of gases.

25. The method of claim 24, wherein the harvest vessel is configured to allow collection of supernatant though a J-tube port into the head space such that the supernatant travels or cascades down the wall(s) of the harvest vessel.

26. The method of claim 25, wherein the supernatant is transmitted onto a surface of the harvest vessel in the head space, and flows along the surface, back to the reservoir culture.

27. The method of claim 26, wherein supernatant travel or cascade in the harvest vessel results in an increase in oxygenation level of the supernatant.

28. The method of claim 23, wherein the DOT of the supernatant is maintained at a range of greater than 40% to less than 500% air saturation in the harvest vessel through surface aeration.

29. The method of claim 23, wherein the harvest vessel comprises a cooling device and mechanism to further cool the reservoir culture to a temperature of 5 °to 8°C.

30. The method of claim 23, wherein the harvest vessel comprises a mixer device capable of axial mixing and an pH titrant addition port.

31. The method of claim 23, wherein the harvest vessel comprises at least one head space gas inlet port and at least one gas outlet port.

32. The method of claim 23, wherein the harvest vessel further comprises at least one air flow controller and at least one O_2 flow controller to provide an air and O_2 mix.

33. The method of claim 23, wherein the harvest vessel comprises sensors that detect DOT, redox, temperature and pH of the supernatant.

34. The method of claim 33, wherein the DOT, redox, temperature and pH sensor output are used to effect change in the sparge rates, head space, and feed or supplement addition into the bioreactor production culture prior to separation; and addition of pH titrant into the harvest vessel.

35. The method of claim 33, wherein the DOT, redox, temperature and pH sensor output are used to effect change addition of pH titrant into the harvest vessel.

36. The method of claim 23, wherein the bioreactor is connected to the harvest vessel using a tubing resistant to occlusion.

37. The method of claim 36, wherein the tubing resistant to occlusion is braided.

38. The method of claim 23, wherein the flow path between the bioreactor and the harvest vessel comprises installations of DOT and redox sensors/probes.

39. The method of claim 38, wherein the DOT and redox sensors/probes output is used to effect change in the sparge rates, head space, and feed or supplement addition into the bioreactor production culture prior to harvest.

40. The method of claim 23, wherein the bioreactor comprises an element configured to deliver culture to a surface defining the headspace of the bioreactor.

41. The method of claim 23, wherein the bioreactor comprises a second element configured to deliver culture to a surface defining the headspace of the bioreactor.

42. The method of claim 1, further comprising monitoring the redox potential of cells within the culture and while isolating the product for the purpose of maintaining the redox potential.

43. The method of claim 42, wherein monitoring the redox potential comprises using in-line monitoring probes.

44. The method of claim 41, wherein monitoring the redox potential comprises evaluating redox status of the cellular factors that impact product stability wherein the cellular factors may compromise an enzyme or metabolic cofactor of the glutathione/reduced glutathione pathway, thioredoxin/reduced thioredoxin pathway, or pentose phosphate pathways selected from glutathione reductase, thioredoxin, glucose-6-phosphate, NADPH, NADP+, 6-phosphonoglucolactone, 6-phosphogluconate, or ribulose-5-phosphate.

45. The method of claim 1 further comprising recovering and purifying the stabilized product.

46. The method of claim 45, wherein the purification step uses chromatography.

47. The method of claim 2 further comprising recovering and purifying the stabilized product.

48. The method of claim 47, wherein the purification step uses chromatography.