

CLAIMS

1. A method of processing a cell culture, the method comprising:
 - (a) providing an open circuit filtration system comprising:
 - a reservoir comprising a cell culture,
 - a tangential flow filtration (TFF) unit having first and second inlets,
 - a first conduit in fluid communication between the reservoir and the TFF unit first inlet, and
 - a second conduit in fluid communication between the reservoir and the TFF unit second inlet, and
 - at least one pump disposed within the system for flowing fluid through the system, wherein the at least one pump is disposed in the reservoir and proximal to the first or second fluid conduit, and wherein the system is configured such that fluid is flowed reversibly through the system from or to the reservoir and through the first and second conduits and the TFF unit via the at least one pump, and filtrate is collected from the TFF unit;
 - (b) flowing the cell culture from the reservoir through the first and second conduits and the TFF unit, and back to the reservoir, in a first flow direction for a first period of time;
 - (c) reversing the first flow direction and flowing the cell culture through the first and second conduits and the TFF unit, and back to the reservoir, in a second flow direction for a second period of time;
 - (d) reversing the second flow direction and flowing the cell culture through the first and second conduits and the TFF unit, and back to the reservoir, in the first flow direction for a third period of time;
 - (e) repeating steps (c) – (d) at least two times; and
 - (f) collecting the filtrate.
2. The method of claim 1, wherein the reservoir is a bioreactor.
3. The method of claim 1, wherein the reservoir is a refrigerated holding tank.
4. The method of claim 1, wherein one or both of the first and second conduits comprise(s) biocompatible tubing.

5. The method of claim 1, wherein the TFF unit comprises a single cross-flow filter.
6. The method of claim 5, wherein the single cross-flow filter is a tubular cross-flow filter.
7. The method of claim 1, wherein the TFF unit comprises two or more cross-flow filters.
8. The method of claim 1, wherein the system further comprises one or more additional TFF units disposed in the first conduit, the second conduit, or both.
9. The method of any one of claims 5-8, wherein the cross-flow filter(s) have an average pore size of 0.2 micrometer.
10. The method of claim 1, wherein the at least one pump is a low turbulence pump (LTP).
11. The method of claim 10, wherein the LTP is a peristaltic pump.
12. The method of claim 10, wherein the system comprises a first and a second LTP, wherein the first LTP flows the cell culture in the first direction and the second LTP flows the cell culture in the second direction.
13. The method of claim 10, wherein the system comprises a single LTP, where the single LTP flows the cell culture in the first direction during the first and third time periods and flows the cell culture in the second direction during the second time period.
14. The method of claim 1, wherein the first, second, and third periods of time are 30 seconds to 15 minutes.
15. The method of claim 1, wherein the cell culture is flowed in one or more of (b), (c), and (d) at a rate of between 0.5 L/minute and 80 L/minute.

16. The method of claim 15, wherein the cell culture is flowed in one or more of (b), (c), and (d) at a rate of between 3.0 L/minute and 60 L/minute.

17. The method of claim 1, wherein a single repetition of (b) and (c) results in an exchange fraction of greater than 50%.

18. The method of claim 1, wherein the filtrate does not contain a mammalian cell.

19. The method of claim 1, wherein the cell culture contains a secreted recombinant protein and the filtrate contains the secreted recombinant protein.

20. The method of claim 19, wherein the secreted recombinant protein is a galactosidase.

21. The method of claim 20, wherein the galactosidase is an α -galactosidase.

22. The method of claim 21, wherein the α -galactosidase is agalactosidase beta.

23. The method of claim 19, wherein the secreted recombinant protein is an antibody or antigen-binding fragment thereof, a growth factor, a cytokine, or an enzyme, or a combination thereof.

24. The method of claim 23, further comprising isolating the secreted recombinant protein from the filtrate.

25. The method of claim 24, wherein isolating is performed using an integrated and continuous process that includes isolating through at least one multi-column chromatography system (MCCS).

26. The method of claim 24, further comprising formulating a therapeutic drug substance by mixing the isolated recombinant protein with a pharmaceutically acceptable excipient or buffer.

27. The method of claim 1, wherein the cell culture or filtrate, or both, are sterile.

28. The method of claim 1, wherein the method is continuously performed for a period of between 14 days to 80 days.

29. An open circuit filtration system comprising:
a reservoir,
a tangential flow filtration (TFF) unit having first and second inlets,
a first conduit in fluid communication between the reservoir and the TFF unit first inlet,
a second conduit in fluid communication between the reservoir and the TFF unit second inlet, and
at least one pump disposed within the system,
wherein actuating the at least one pump flows fluid reversibly through the system from the reservoir, through the first conduit, the TFF unit, the second conduit, and back to the reservoir, wherein the at least one pump is disposed in the reservoir and proximal to the first or second fluid conduit.

30. The open circuit filtration system of claim 29, wherein the reservoir is a bioreactor.

31. The open circuit filtration system of claim 29, wherein the reservoir is a refrigerated holding tank.

32. The open circuit filtration system of claim 29, wherein one or both of the first and second conduits comprise(s) biocompatible tubing.

33. The open circuit filtration system of claim 29, wherein the TFF unit comprises a single cross-flow filter.

34. The open circuit filtration system of claim 33, wherein the single cross-flow filter is a tubular cross-flow filter.

35. The open circuit filtration system of claim 29, wherein the TFF unit comprises two or more cross-flow filters.

36. The open circuit filtration system of claim 29, wherein the system further comprises one or more additional TFF units disposed in the first conduit, the second conduit, or both.

37. The open circuit filtration system of any one of claims 33-36, wherein the cross-flow filter(s) have an average pore size of 0.2 micrometer.

38. The open circuit filtration system of claim 29, wherein the at least one pump is a low turbulence pump (LTP).

39. The open circuit filtration system of claim 38, wherein the LTP is a peristaltic pump.

40. The open circuit filtration system of claim 38, wherein the system comprises a first and a second LTP, wherein the first LTP is adapted to flow the cell culture in a first flow direction and the second LTP is adapted to reverse the first flow direction and flow the cell culture in a second flow direction.

41. The open circuit filtration system of claim 38, wherein the system comprises a single LTP adapted to reversibly flow the cell culture in a first and second flow directions.

42. The open filtration system of claim 39, wherein the peristaltic pump has a pump head volume of between 20 mL and 250 mL.

43. The open filtration system of claim 29, further comprising a filtrate holding tank and a filtrate conduit in fluid communication between the TFF unit and the filtrate holding tank.

44. The open filtration system of claim 29, further comprising a biological manufacturing system comprising at least one multi-column chromatography system (MCCS) and an inlet and an outlet and a filtrate conduit in fluid communication between the TFF unit and the inlet of the biological manufacturing system, wherein the device is configured such that filtrate is passed into the inlet of the biological manufacturing system, through the at least

one MCCS, and exits the device through the outlet of the biological manufacturing system.

45. The open filtration system of claim 29, wherein the TFF unit is disposed in a housing.

46. A method of processing a cell culture, the method comprising:

(a) providing an open circuit filtration system comprising:

a reservoir comprising a cell culture,

a tangential flow filtration (TFF) unit having first and second inlets,

a first conduit in fluid communication between the reservoir and the TFF unit first inlet, and

a second conduit in fluid communication between the reservoir and the TFF unit second inlet, and

at least one pump disposed within the system for flowing fluid through the system,

wherein the system further comprises one or more additional TFF units disposed in the first conduit, the second conduit, or both, and the at least one pump is disposed in the system between any two TFF units, and wherein the system is configured such that fluid is flowed reversibly through the system from or to the reservoir and through the first and second conduits and the TFF units via the at least one pump, and filtrate is collected from the TFF units;

(b) flowing the cell culture from the reservoir through the first and second conduits and the TFF units, and back to the reservoir, in a first flow direction for a first period of time;

(c) reversing the first flow direction and flowing the cell culture through the first and second conduits and the TFF units, and back to the reservoir, in a second flow direction for a second period of time;

(d) reversing the second flow direction and flowing the cell culture through the first and second conduits and the TFF units, and back to the reservoir, in the first flow direction for a third period of time;

(e) repeating steps (c) – (d) at least two times; and

(f) collecting the filtrate.

47. The method of claim 46, wherein the reservoir is a bioreactor.
48. The method of claim 46, wherein the reservoir is a refrigerated holding tank.
49. The method of claim 46, wherein one or both of the first and second conduits comprise(s) biocompatible tubing.
50. The method of claim 46, wherein the TFF units comprise a single cross-flow filter.
51. The method of claim 50, wherein the single cross-flow filter is a tubular cross-flow filter.
52. The method of claim 50, wherein the TFF units comprise two or more cross-flow filters.
53. The method of any one of claims 50-52, wherein the cross-flow filter(s) have an average pore size of 0.2 micrometer.
54. The method of claim 46, wherein the at least one pump is a low turbulence pump (LTP).
55. The method of claim 54, wherein the LTP is a peristaltic pump.
56. The method of claim 54, wherein the system comprises a first and a second LTP, wherein the first LTP flows the cell culture in the first direction and the second LTP flows the cell culture in the second direction.
57. The method of claim 54, wherein the system comprises a single LTP, where the single LTP flows the cell culture in the first direction during the first and third time periods and flows the cell culture in the second direction during the second time period.
58. The method of claim 46, wherein the first, second, and third periods of time are 30 seconds to 15 minutes.

59. The method of claim 46, wherein the cell culture is flowed in one or more of (b), (c), and (d) at a rate of between 0.5 L/minute and 80 L/minute.

60. The method of claim 59, wherein the cell culture is flowed in one or more of (b), (c), and (d) at a rate of between 3.0 L/minute and 60 L/minute.

61. The method of claim 46, wherein a single repetition of (b) and (c) results in an exchange fraction of greater than 50%.

62. The method of claim 46, wherein the filtrate does not contain a mammalian cell.

63. The method of claim 46, wherein the cell culture contains a secreted recombinant protein and the filtrate contains the secreted recombinant protein.

64. The method of claim 63, wherein the secreted recombinant protein is a galactosidase.

65. The method of claim 64, wherein the galactosidase is an α -galactosidase.

66. The method of claim 65, wherein the α -galactosidase is agalasinase beta.

67. The method of claim 63, wherein the secreted recombinant protein is an antibody or antigen-binding fragment thereof, a growth factor, a cytokine, or an enzyme, or a combination thereof.

68. The method of claim 67, further comprising isolating the secreted recombinant protein from the filtrate.

69. The method of claim 68, wherein isolating is performed using an integrated and continuous process that includes isolating through at least one multi-column chromatography system (MCCS).

70. The method of claim 68, further comprising formulating a therapeutic drug substance by mixing the isolated recombinant protein with a pharmaceutically acceptable excipient or buffer.

71. The method of claim 46, wherein the cell culture or filtrate, or both, are sterile.

72. The method of claim 46, wherein the method is continuously performed for a period of between 14 days to 80 days.

73. An open circuit filtration system comprising:
a reservoir,
a tangential flow filtration (TFF) unit having first and second inlets,
a first conduit in fluid communication between the reservoir and the TFF unit first inlet,
a second conduit in fluid communication between the reservoir and the TFF unit second inlet,
at least one pump disposed within the system, and
one or more additional TFF units disposed in the first conduit, the second conduit, or both,
wherein:
the at least one pump is disposed in the system between any two TFF units; and

actuating the at least one pump flows fluid reversibly through the system from the reservoir, through the first conduit, the TFF units, the second conduit, and back to the reservoir.

74. The open circuit filtration system of claim 73, wherein the reservoir is a bioreactor.

75. The open circuit filtration system of claim 73, wherein the reservoir is a refrigerated holding tank.

76. The open circuit filtration system of claim 73, wherein one or both of the first and second conduits comprise(s) biocompatible tubing.

77. The open circuit filtration system of claim 73, wherein the TFF units comprise a single cross-flow filter.

78. The open circuit filtration system of claim 77, wherein the single cross-flow filter is a tubular cross-flow filter.

79. The open circuit filtration system of claim 73, wherein the TFF units comprise two or more cross-flow filters.

80. The open circuit filtration system of any one of claims 77-79, wherein the cross-flow filter(s) have an average pore size of 0.2 micrometer.

81. The open circuit filtration system of claim 73, wherein the at least one pump is a low turbulence pump (LTP).

82. The open circuit filtration system of claim 81, wherein the LTP is a peristaltic pump.

83. The open circuit filtration system of claim 81, wherein the system comprises a first and a second LTP, wherein the first LTP is adapted to flow the cell culture in a first flow direction and the second LTP is adapted to reverse the first flow direction and flow the cell culture in a second flow direction.

84. The open circuit filtration system of claim 81, wherein the system comprises a single LTP adapted to reversibly flow the cell culture in a first and second flow directions

85. The open filtration system of claim 82, wherein the peristaltic pump has a pump head volume of between 20 mL and 250 mL.

86. The open filtration system of claim 73, further comprising a filtrate holding tank and a filtrate conduit in fluid communication between the TFF units and the filtrate holding tank.

87. The open filtration system of claim 73, further comprising a biological manufacturing system comprising at least one multi-column chromatography system (MCCS) and an inlet and an outlet and a filtrate conduit in fluid communication between the TFF units and the inlet of the biological manufacturing system, wherein the device is configured such that filtrate is passed into the inlet of the biological manufacturing system, through the at least one MCCS, and exits the device through the outlet of the biological manufacturing system.

88. The open filtration system of claim 73, wherein the TFF units are disposed in a housing.