

WHAT IS CLAIMED IS:

1. An isolated eukaryotic cell line, wherein the cell line comprises a stable integrated loss-of-function or attenuation-of-function mutation in each of the *Bax* and *Bak* genes.
2. The cell line of claim 1, wherein the cell line comprises a stable integrated loss-of-function mutation in each of the *Bax* and *Bak* genes.
3. The cell line of claim 1 or claim 2, wherein the cell line is an animal cell line or a fungal cell line.
4. The cell line of claim 3, wherein the animal cell line is a mammalian cell line.
5. The cell line of claim 4, wherein the mammalian cell line is a COS cell line, a VERO cell line, a HeLa cell line, a HEK 293 cell line, a PER-C6 cell line, a K562 cell line, a MOLT-4 cell line, a M1 cell line, a NS-1 cell line, a COS-7 cell line, a MDBK cell line, a MDCK cell line, a MRC-5 cell line, a WI-38 cell line, a WEHI cell line, a SP2/0 cell line, a BHK cell line or a CHO cell line, or their derivatives.
6. The cell line of claim 5, wherein the CHO cell line is a CHO K1 cell line, a CHO K1SV cell line, a DG44 cell line, a DUKXB-11 cell line, a CHOK1S cell line, or a CHO K1M cell line, or their derivatives.
7. The cell line of any preceding claim, wherein the cell line comprises a deletion in each of the *Bax* and *Bak* genes.
8. The cell line of any preceding claim, wherein the cell line further comprises a viral genome and one or more polynucleotides encoding a viral capsid.
9. The cell line of any preceding claim, wherein the cell line further comprises a polynucleotide encoding a product of interest.
10. The cell line of claim 9, wherein the polynucleotide that encodes the product of interest is integrated in the cellular genome of the cell line at a targeted location.
11. The cell line of claim 9, wherein the polynucleotide that encodes the product of interest is randomly integrated in the cellular genome of the cell line.
12. The cell line of any of claims 9-11, wherein the polynucleotide that encodes the product of interest is an extrachromosomal polynucleotide.
13. The cell line of any of claims 9-11, wherein the polynucleotide that encodes the product of interest is integrated into a chromosome of the cell line.

14. The cell line of any of claims 9-11, wherein product of interest comprises a recombinant polypeptide.
15. The cell line of any of claims 9-14, wherein the product of interest comprises an antibody, an antibody-fusion protein, an antigen, an enzyme, or a vaccine.
16. The cell line of claim 15, wherein the antibody is a multispecific antibody or antigen-binding fragment thereof.
17. The cell line of claim 15 or claim 16, wherein the antibody consists of a single heavy chain sequence and a single light chain sequence or antigen-binding fragments thereof.
18. The cell line of any of claims 15-17, wherein the antibody comprises a chimeric antibody, a human antibody or a humanized antibody.
19. The cell line of any of claims 15-18, wherein the antibody comprises a monoclonal antibody.
20. The cell line of any of claims 7-19, wherein the cell line has a higher specific productivity than a corresponding isolated eukaryotic cell line that comprises the polynucleotide and functional copies of each of the wild type *Bax* and *Bak* genes.
21. The cell line of any preceding claim, wherein the cell line is more resistant to apoptosis than a corresponding isolated eukaryotic cell line that comprises functional copies of each of the *Bax* and *Bak* genes.
22. The cell line of any preceding claim, wherein the cell line is employed in cell culture processes such as fed-batch, perfusion, process intensified, semi-continuous perfusion, or continuous perfusion.
23. The cell line of claim 22, wherein the cell line is employed in an intensified perfusion process.
24. A composition comprising a eukaryotic cell line according to any preceding claim.
25. The composition of claim 24, further comprising a cell culture medium.
26. A cell culture comprising a cell culture medium and a plurality of eukaryotic cells, wherein each cell of the plurality comprises a stable integrated loss-of-function or attenuation-of-function mutation in each of the *Bax* and *Bak* genes.

27. The cell culture of claim 26, wherein each cell comprises a stable integrated loss-of-function mutation in each of the *Bax* and *Bak* genes.
28. The cell culture of claim 26 or claim 27, wherein each cell of the plurality comprises a deletion in each of the *Bax* and *Bak* genes.
29. The cell culture of any of claims 26-28, wherein the cells are animal cells or fungal cells.
30. The cell culture of claim 29, wherein the animal cells are mammalian cells.
31. The cell culture of claim 30, wherein the mammalian cells are COS cells, VERO cells, HeLa cells, HEK 293 cells, PER-C6 cells, K562 cells, MOLT-4 cells, M1 cells, NS-1 cells, COS-7 cells, MDBK cells, MDCK cells, MRC-5 cells, WI-38 cells, WEHI cells, SP2/0 cells, BHK cells or a CHO cells, or their derivatives.
32. The cell culture of claim 31, wherein the CHO cells are a CHO K1 cells, CHO K1SV cells, DG44 cells, DUKXB-11 cells, CHOK1S cells, or CHO K1M cells, or their derivatives.
33. The cell culture of any of claims 26-32, wherein the cell culture further comprises a polynucleotide that encodes a product of interest.
34. The cell culture of claim 33, wherein the polynucleotide that encodes the product of interest is integrated in the cellular genome of the cells at a targeted location.
35. The cell culture of claim 33, wherein the polynucleotide that encodes the product of interest is randomly integrated in the cellular genome of the cells.
36. The cell culture of any of claims 33-35, wherein the polynucleotide that encodes the product of interest is an extrachromosomal polynucleotide.
37. The cell culture of any of claims 33-35, wherein the polynucleotide that encodes the product of interest is integrated into a chromosome of the cells.
38. The cell culture of any of claims 33-37, wherein the product of interest comprises a recombinant polypeptide.
39. The cell culture of any of claims 33-38, wherein the product of interest is an antibody, an antibody-fusion protein, an antigen, an enzyme, or a vaccine.
40. The cell culture of claim 39, wherein the antibody is a multispecific antibody or antigen-binding fragment thereof.

41. The cell culture of claim 39 or claim 40, wherein the antibody consists of a single heavy chain sequence and a single light chain sequence or antigen-binding fragments thereof.
42. The cell culture of any of claims 39-41, wherein the antibody comprises a chimeric antibody, a human antibody or a humanized antibody.
43. The cell culture of any of claims 39-42, wherein the antibody comprises a monoclonal antibody.
44. The cell culture of any of claims 26-43, wherein the each of the cells further comprise a recombinant polynucleotide.
45. The cell culture of claims 26-44, wherein the cells are employed in a cell culture process such as fed-batch, perfusion, process intensified, semi-continuous perfusion, or continuous perfusion.
46. The cell culture of claim 45, wherein the cells are employed in an intensified perfusion process.
47. A method of reducing apoptotic activity in a eukaryotic cell, comprising administering to the cell a genetic engineering system, wherein the genetic engineering system:
 - a. knocks down or knocks out the expression of a *Bax* polypeptide isoform;
and
 - b. knocks down or knocks out the expression of a *Bak* polypeptide isoform.
48. The method of claim 47, wherein the method further comprises employing the eukaryotic cell in a fed-batch, perfusion, process intensified, semi-continuous perfusion, or continuous perfusion cell culture process.
49. The method of claim 48, wherein the eukaryotic cell is employed in an intensified cell culture process.
50. The method of any of claims 47-49, wherein the genetic engineering system is selected from the group consisting of a CRISPR/Cas system, a zinc-finger nuclease (ZFN) system, a transcription activator-like effector nuclease (TALEN) system and a combination thereof.
51. The method of any of claims 47-50, wherein the genetic engineering system is or comprises a CRISPR/Cas9 system.

52. The method of claim 51, wherein the CRISPR/Cas9 system comprises:
- a. a Cas9 molecule,
 - b. at least one first guide RNA (gRNA) comprising a targeting sequence that is complementary to a target sequence in a *Bax* gene, and
 - c. at least one second gRNA comprising a targeting sequence that is complementary to a target sequence in a *Bak* gene.
53. The method of claim 52, wherein at least one of the target sequences is a portion of the *Bax* gene, and/or wherein at least one of the target sequences is a portion of the *Bak* gene.
54. The method of any of claims 47-53, wherein the expression of the *Bax* polypeptide and/or the expression of the *Bak* polypeptide is knocked out, and the apoptotic activity of the cell is reduced compared to the apoptotic activity of a reference cell.
55. The method of any of claims 47-53, wherein the expression of the *Bax* polypeptide and/or the expression of the *Bak* polypeptide is knocked down, and the apoptotic activity of the cell is reduced compared to the apoptotic activity of a reference cell.
56. The method of claim 54 or claim 55, wherein the apoptotic activity of the cell is determined from the viability for a population of said cells compared to the viability of a population of said reference cells determined at day 14 of a production phase.
57. The method of any of claims 54-56, wherein the reference cell is a cell that comprises wild-type alleles of the *Bax* and *Bak* genes.
58. The method of any of claims 47-57, wherein the genetic engineering system is or comprises a zinc-finger nuclease (ZFN) system or a transcription activator-like effector nuclease (TALEN) system.
59. The method of any of claims 47-58, wherein the cell line development system comprises targeted integration, random integration or transposase systems.
60. The method of any of claims 47-59, wherein the cell is an animal cell or a fungal cell.
61. The method of claim 60, wherein the animal cell is a mammalian cell.
62. The method of claim 61, wherein the mammalian cell is a COS cell, a VERO cell, a HeLa cell, a HEK 293 cell, a PER-C6 cell, a K562 cell, a MOLT-4 cell, a M1 cell,

- NS-1 cell, a COS-7 cell, a MDBK cell, a MDCK cell, a MRC-5 cell, a WI-38 cell, a WEHI cell, a SP2/0 cell line, a BHK cell or a CHO cell line, or their derivatives.
63. The method of claim 62, wherein the CHO cell is a CHO K1 cell, a CHO K1SV cell, a DG44 cell, a DUKXB-11 cell, a CHOK1S cell, or a CHO K1M cell, or their derivatives.
64. The method of any of claims 47-63, wherein the cell further comprises a polynucleotide that encodes a product of interest.
65. The method of claim 64, wherein the polynucleotide that encodes the product of interest is integrated in the cellular genome of the cell at a targeted location.
66. The method of claim 64, wherein the polynucleotide that encodes the product of interest is randomly integrated in the cellular genome of the cell.
67. The method of any of claims 64-66, wherein the polynucleotide that encodes the product of interest is an extrachromosomal polynucleotide.
68. The method of any of claims 64-66, wherein the polynucleotide that encodes the product of interest is integrated into a chromosome of the cell.
69. The method of any of claims 64-68, wherein the product of interest comprises a recombinant polypeptide.
70. The method of any of claims 64-69, wherein the product of interest is an antibody, an antibody-fusion protein, an antigen, an enzyme, or a vaccine.
71. The method of claim 70, wherein the antibody is a multispecific antibody or antigen-binding fragment thereof.
72. The method of claim 70 or claim 71, wherein the antibody consists of a single heavy chain sequence and a single light chain sequence or antigen-binding fragments thereof.
73. The method of any of claims 70-72, wherein the antibody comprises a chimeric antibody, a human antibody or a humanized antibody.
74. The method of any of claims 70-73, wherein the antibody comprises a monoclonal antibody.
75. The method of any of claims 70-74, wherein the each of the cells further comprise a recombinant polynucleotide.

76. A method of producing a recombinant polypeptide, comprising:
- culturing a eukaryotic cell line that comprises:
- (a) a stable integrated loss-of-function or attenuation-of-function mutation in each of the *Bax* and *Bak* genes, and
- (b) a polynucleotide encoding the recombinant polypeptide,
- under conditions suitable for production of the polypeptide.
77. The method of claim 76, wherein the polynucleotide that encodes the polypeptide is integrated in the cellular genome of the cells of the cell line at a targeted location.
78. The method of claim 76, wherein the polynucleotide that encodes the polypeptide is randomly integrated in the cellular genome of the cells of the cell line.
79. The method of any of claims 76-78, wherein the polynucleotide that encodes the polypeptide is an extrachromosomal polynucleotide.
80. The method of any of claims 76-79, wherein the polynucleotide that encodes the polypeptide is integrated into a chromosome of the cells of the cell line.
81. The method of any of claims 76-80, wherein the recombinant polypeptide is an antibody, an antibody-fusion protein, an antigen, an enzyme, or a vaccine.
82. The method of claim 81, wherein the antibody is a multispecific antibody or antigen-binding fragment thereof.
83. The method of claim 81 or claim 82, wherein the antibody consists of a single heavy chain sequence and a single light chain sequence or antigen-binding fragments thereof.
84. The method of any of claims 81-83, wherein the antibody comprises a chimeric antibody, a human antibody or a humanized antibody.
85. The method of any of claims 81-84, wherein the antibody comprises a monoclonal antibody.
86. The method of any of claims 76-85, further comprising isolating the recombinant polypeptide.
87. A method of producing a viral vector, comprising:

culturing a eukaryotic cell line that comprises (a) stable integrated a loss-of-function or attenuation-of function mutation in each of the *Bax* and *Bak* genes, (b) a viral genome, and (c) one or more polynucleotides encoding a viral capsid, under conditions suitable for production of the viral vector.

88. The method of claim 87, further comprising isolating the viral vector.
89. The method of any of claims 87-88, wherein the cell line is an animal cell line, or a fungal cell line.
90. The method of claim 89, wherein the animal cell line is a mammalian cell line.
91. The method of claim 90, wherein the mammalian cell line is a COS cell line, a VERO cell line, a HeLa cell line, a HEK 293 cell line, a PER-C6 cell line, a K562 cell line, a MOLT-4 cell line, a M1 cell line, a NS-1 cell line, a COS-7 cell line, a MDBK cell line, a MDCK cell line, a MRC-5 cell line, a WI-38 cell line, a WEHI cell line, a SP2/0 cell line, a BHK cell line or a CHO cell line, or their derivatives.
92. The method of claim 91, wherein the CHO cell line is a CHO K1 cell line, a CHO K1SV cell line, a DG44 cell line, a DUKXB-11 cell line, a CHOK1S cell line, or a CHO K1M cell line, or their derivatives.
93. The method of any of claims 87-92, wherein the cell line is cultured in a cell culture medium.
94. The method of any of claims 87-93, wherein the cell line is cultured under fed-batch culture conditions, or perfusion culture conditions.
95. The method of claim 94, wherein the cell line is cultured under fed-batch culture conditions, optionally wherein the fed-batch culture conditions are intensified fed-batch culture conditions.
96. The method of any of claims 87-95, wherein the cell line is cultured under perfusion culture conditions, optionally wherein the perfusion culture conditions are semi-continuous perfusion or continuous perfusion.
97. The method of any of claims 87-96, wherein the cell line comprises a stable integrated loss-of-function mutation in each of the *Bax* and *Bak* genes.