WE CLAIM:

1. A method of generating a cell line that has reduced apoptosis for incorporating a non-natural amino acid into a protein, the method comprising inactivating one or more target site(s) or region(s) in a cell, wherein the one or more target site(s) or region(s) is a pro-apoptotic gene involved in an apoptotic pathway, wherein the pro-apoptotic gene is selected from Bax and Bak, wherein the cell expresses a selector codon-containing gene of interest, and wherein the cell comprises an orthogonal aminoacyl tRNA synthetase (O-RS), and an orthogonal suppressor tRNA (O-tRNA).

2. The method of claim 1, further comprising providing a nucleic acid molecule capable of inactivating the one or more target site(s) or region(s) in the cell, and introducing the nucleic acid molecule into the cell, wherein the nucleic acid molecule inactivates the one or more target site(s) or region(s), optionally wherein the nucleic acid molecule is selected from SEQ ID NOs: 1-6.

3. The method of claim 1 or claim 2, wherein:

a) the cell line is:

(i) a eukaryotic cell line; and/or

(ii) selected from a transient cell line, a stable cell line population or a stable clonal cell line, optionally wherein the stable cell line population is a platform or production cell line; or

b) the cell line is selected from COS, CHO, VERO, MDCK, WI38, V79, Bl4AF28-G3, BHK, HaK, NSO, SP2/0-Agl4, HeLa, or HEK293.

4. The method of any one of claims 1-3, wherein:

a) the non-natural amino acid is selected from para-acetyl phenylalanine, p-nitrophenylalanine, p-sulfotyrosine, p-carboxyphenylalanine, o-nitrophenylalanine, m-nitropheny lalanine, p-borony1 phenylalanine, o-borony1phenylalanine, m-boronylphenylalanine, p-aminopheny lalanine, o-aminopheny lalanine, m-aminopheny lalanine, p-acylphenylalanine, o-acylphenylalanine, m-acylphenylalanine, *p-OMe* phenylalanine, o-OMe

phenylalanine, m-OMe phenylalanine, p-sulfophenylalanine, o-sulfophenylalanine, m-sulfophenylalanine, 5-nitro His, 3-nitro Tyr, 2-nitro Tyr, nitro substituted Leu, nitro substituted His, nitro substituted De, nitro substituted Trp, 2-nitro Trp, 4-nitro Trp, 5-nitro Trp, 6-nitro Trp, 7-nitro Trp, 3-aminotyrosine, 2-aminotyrosine, O-sulfotyrosine, 2-sulfooxyphenylalanine, 3-sulfooxyphenylalanine, o-carboxyphenylalanine, m-carboxyphenylalanine, p-acetyl-L-phenylalanine, p-propargyl-phenylalanine, O-methy1-L-tyrosine, L-3-(2-naphthy1)alanine, 3-methy1-phenylalanine, O-4-ally1-L-tyrosine, 4-propy1-L-tyrosine, tri-O-acety1-GlcNAc -serine, L-Dopa, fluorinated phenylalanine, isopropy1-L-phenylalanine, p-azido-L-phenylalanine, p-acy1-L-phenylalanine, p-benzoyl-L-phenylalanine, L-phosphoserine, phosphonoserine, phosphonotyrosine, p-iodo-phenylalanine, p-bromophenylalanine, p-amino-L-phenylalanine, isopropyl-L-phenylalanine and p-propargyloxy-L-phenylalanine; and/or

b) the non-natural amino acid is site specifically incorporated into said protein.

5. The method of any one of claims 1-4, wherein the gene of interest is a biotherapeutic gene or product, optionally wherein the biotherapeutic gene or product is a vaccine.

6. The method of any one of claims 1-5, wherein the gene of interest encodes:

a) an antibody, scFv, scFv fusion protein, Fc fusion protein, Factor VII, Factor VIII, or Factor IV;

b) a cytokine, interleukin, interferon, chemokine, growth factor, hormone, or a receptor, analog, bispecific or fragment thereof; or

c) HER2, CD-70, PSMA, 5T4, EGFR, TROP2, CD3, IL-2, IL-3, IL-10, IL-15, GPC3, DLL3, RORI, leptin, FGF-21, FGF-23, HGH, FcR, insulin, TNFRI, TRAIL, EPO, or an analog, bispecific or fragment thereof.

7. The method of any one of claims 1-6, wherein:

a) the one or more target site(s) or region(s) is fully or partially inactivated;

b) the one or more target site(s) or region(s) is the same or different;

c) the selector codon is a nonsense codon, a rare codon, a fourbase codon; and/or

d) the selector codon is an ochre codon, an opal codon, or an amber codon.

8. The method of any one of claims 1-7, for optimizing the yield of a non-natural amino acid containing protein in the cell line, optionally wherein the yield of the non-natural amino acid containing protein is at least 0.5-fold or greater than in the absence of inactivating the one or more target site(s) or region(s).

9. A method of decreasing or reducing apoptosis in a cell, wherein the cell expresses a selector codon-containing gene of interest, and wherein the cell comprises an orthogonal aminoacyl tRNA synthetase (O-RS) and an orthogonal suppressor tRNA (O-tRNA), the method comprising inactivating one or more pro-apoptotic target site(s) or region(s) in the cell, wherein the one or more pro-apoptotic target site(s) or region(s) is selected from Bax and Bak.

10. A method of generating a cell or cell line that has reduced apoptosis for incorporating a non-natural amino acid into a protein, the method comprising: providing a cell or cell line expressing a selector codon-containing gene of interest, and comprising an orthogonal aminoacyl tRNA synthetase (O-RS) and an orthogonal suppressor tRNA (O-tRNA); introducing into the cell line a nucleic acid molecule capable of inactivating one or more target site(s) or region(s) in the cell or cell line, wherein the one or more target site(s) or region(s) is a pro-apoptotic gene involved in an apoptotic pathway, wherein the pro-apoptotic gene is selected from Bax and Bak; optionally wherein the nucleic acid molecule is selected from SEQ ID NOs: 1-6, and further optionally providing a non-natural amino acid to the cell or cell line.

11. The method of any one of claims 1-10, comprising inactivating both Bax and Bak, and wherein the gene of interest encodes an antibody.

12. A cell or cell line that has reduced apoptosis for incorporating a non-natural amino acid into a protein, wherein the cell expresses a selector codon-containing gene of interest, wherein the cell comprises an orthogonal aminoacyl tRNA synthetase (O-RS), and an orthogonal suppressor tRNA (O-tRNA); and wherein the cell comprises one or more inactivated target site(s) or region(s), wherein the one or more inactivated target site(s) or region(s) is a pro-apoptotic gene involved in an apoptotic pathway, wherein the pro-apoptotic gene is selected from Bax and Bak.

13. The cell or cell line of claim 12, comprising a nucleic acid molecule capable of inactivating the one or more target site(s) or region(s) in the cell, optionally wherein the nucleic acid molecule is selected from SEQ ID NOs: 1-6.

14. The cell or cell line of claim 12 or claim 13, wherein:

a) the cell or cell line is:

(i) a eukaryotic cell line; and/or

(ii) selected from a transient cell line, a stable cell line population or a stable clonal cell line, optionally wherein the stable cell line population is a platform or production cell line; or

b) the cell or cell line is selected from COS, CHO, VERO, MDCK, WI38, V79, Bl4AF28-G3, BHK, HaK, NSO, SP2/0-Agl4, HeLa, or HEK293; and/or

c) the selector codon is:

(i) a nonsense codon, a rare codon, a fourbase codon; or

(ii) an ochre codon, an opal codon, or an amber codon.

15. The cell or cell line of any one of claims 12-14, wherein the gene of interest is a biotherapeutic gene or product, optionally wherein the biotherapeutic gene or product is a vaccine.

16. The cell or cell line of any one of claims 12-15, wherein the gene of interest encodes:

a) an antibody, scFv, scFv fusion protein, Fc fusion protein, Factor VII, Factor VIII, or Factor IV;

b) a cytokine, interleukin, interferon, chemokine, growth factor, hormone, or a receptor, analog, bispecific or fragment thereof; or

c) HER2, CD-70, PSMA, 5T4, EGFR, TROP2, CD3, IL-2, IL-3, IL-10, IL-15, GPC3, DLL3, RORI, leptin, FGF-21, FGF-23, HGH, FcR, insulin, TNFRI, TRAIL, EPO, or an analog, bispecific or fragment thereof.

17. The cell or cell line of any one of claims 12-16, wherein both Bax and Bak are inactivated, and wherein the gene of interest encodes an antibody.