CLAIMS

What is claimed is:

1. A method of recombinant production of an antibody, the method comprising:
   (a) expressing a nucleic acid encoding an antibody in a modified cell line, wherein the antibody specifically binds to a target epitope on a target protein that is natively expressed as an intracellular protein in the cell; and wherein the modified cell is engineered to express a variant target protein that comprises a mutation of one or more amino acid residues of the target epitope; and
   (b) culturing the modified cell line under conditions so that the antibody is produced.

2. The method of claim 1, further comprising (c) isolating the antibody from the culture supernatant.

3. The method of claim 1 or claim 2, wherein the target protein that is natively expressed is an intracellular protein in the secretory pathway of the cell line.

4. The method of any of claims 1-3, wherein the mutation is an inert mutation that retains the structure and function of the native target protein in the cell.

5. The method of any of claims 1-4, wherein the mutation reduces or abrogates binding of the antibody to the target epitope on the target protein.

6. The method of any of claims 1-5, wherein the target protein is a stress protein.

7. The method of any of claims 1-6, wherein the target protein is expressed on an organelle of the cell line.

8. The method of claim 7, wherein the organelle is the endoplasmic reticulum or the Golgi apparatus.

9. The method of any of claims 1-8, wherein the target protein is an endoplasmic reticulum chaperone.

10. The method of claim 9, wherein the endoplasmic reticulum chaperone is a calreticulin, a heat shock protein or an isomerase.

11. The method of any of claims 1-10, wherein the target protein is glucose-regulated protein 78 (GRP78), HSP47, PDI, calreticulin or GP94.

12. The method of any of claims 1-11, wherein the target protein is glucose-regulated protein 78 (GRP78).

13. The method of any of claims 1-8, wherein the target protein is a Golgi complex protein.

14. The method of claim 13, wherein the Golgi complex protein is GOLPH2, GOLPH3, GM130, ATP6V1A, ATP6V1E1, ATP6VOA2, TMEM165, GOLGB1, SCYL1BP1, TRAPPC11, TRAPPC2 or TRIP11.

15. A method of recombinant production of an antibody, the method comprising:
    (a) expressing a nucleic acid encoding an antibody in a modified mammalian cell line, wherein the antibody specifically binds a target epitope on a target protein that is natively expressed as an intracellular protein in the mammalian cell line and wherein the modified mammalian cell line is engineered to express a variant target protein that comprises a mutation of one or more amino acid residues of the target epitope; and
    (b) culturing the modified mammalian cell line under conditions so that the antibody is produced.

16. The method of claim 15, further comprising (c) isolating the antibody from the culture supernatant.

17. The method of claim 15 or claim 16, wherein the target protein that is natively expressed is an intracellular protein in the secretory pathway of the mammalian cell line.

18. The method of any of claims 15-17, wherein the mutation is an inert mutation that retains the structure and function of the target protein in the mammalian cell line.

19. The method of any of claims 15-18, wherein the mutation reduces or abrogates binding of the antibody to the target epitope on the target.

20. The method of any of claims 15-19, wherein the target protein is a stress protein.

21. The method of any of claims 15-20, wherein the target protein is expressed on an organelle of the mammalian cell line.

22. The method of claim 21, wherein the organelle is the endoplasmic reticulum or the Golgi apparatus.

23. The method of any of claims 15-22, wherein the target protein is an endoplasmic reticulum chaperone.

24. The method of claim 23, wherein the endoplasmic reticulum chaperone is a calreticulin, a heat shock protein or an isomerase.

25. The method of any of claims 15-24, wherein the target protein is glucose-regulated protein 78 (GRP78), HSP47, PDI, calreticulin or GP94.

26. The method of any of claims 15-25, wherein the target protein is glucose-regulated protein 78 (GRP78).

27. The method of any of claims 15-22, wherein the target protein is a Golgi complex protein.

28. The method of claim 27, wherein the Golgi complex protein is GOLPH2, GOLPH3, GM130, ATP6V1A, ATP6V1E1, ATP6VOA2, TMEM165, GOLGB1, SCYL1BP1, TRAPPC11, TRAPPC2 or TRIP11.

29. A method of recombinant production of an antibody targeting an epitope on a target protein found intracellularly in a cell line, the method comprising:
    (a) providing an antibody that binds to an epitope on a target protein that is present intracellularly in a cell line;
    (b) identifying the epitope of the target protein to which the antibody binds;
    (c) generating a modified cell line by mutating the epitope of the target protein in the cell line to reduce or abrogate the binding of the antibody to the epitope on the target protein;
    (d) introducing an expression vector encoding the antibody to the modified cell line;
    (e) culturing the modified cell line under conditions that allow production of the antibody from the expression vector; and
    (f) expressing a nucleic acid encoding an antibody in the modified cell line.

30. The method of claim 29, wherein the produced antibody is secreted to the culture supernatant.

31. The method of claim 29 or claim 30, further comprising (g) isolating the antibody or antigen binding fragment.

32. The method of any of claims 29-31, wherein the antibody is a humanized antibody.

33. The method of any of claims 29-31, wherein the antibody is a human antibody.

34. The method of any of claims 29-33, wherein the target protein that is present intracellularly in the cell line is an intracellular protein in the secretory pathway of the cell line.

35. The method of any of claims 29-34, wherein the target protein is a stress protein.

36. A method of recombinant production of an antibody targeting an epitope on a target protein found intracellularly in a mammalian cell line, the method comprising:
    (a) providing an antibody that binds to an epitope on a target protein that is present intracellularly in a mammalian cell line;
    (b) identifying the epitope of the target protein to which the antibody binds;
    (c) generating a modified cell line by mutating the epitope of the target protein in the mammalian cell line to reduce or abrogate the binding of the antibody to the epitope on the target protein;
    (d) introducing an expression vector encoding the antibody to the modified mammalian cell line;
    (e) culturing the modified mammalian cell line under conditions that allow production of the antibody from the expression vector; and
    (f) expressing a nucleic acid encoding an antibody in the modified mammalian cell line.

37. The method of claim 36, wherein the produced antibody is present in the culture supernatant.

38. The method of claim 37, further comprising (g) isolating the antibody or antigen binding fragment.

39. The method of any of claims 36-38, wherein the antibody is a humanized antibody.

40. The method of any of claims 36-38, wherein the antibody is a human antibody.

41. The method of any of claims 36-40, wherein the target protein that is present intracellularly in the mammalian cell line is an intracellular protein in the secretory pathway of the mammalian cell line.

42. The method of any of claims 40-41, wherein the target protein is a stress protein.

43. A method of recombinant production of an antibody targeting GRP78, the method comprising:
    (a) expressing a nucleic acid encoding an antibody in a modified mammalian cell line, wherein the antibody binds to GRP78 and wherein the modified mammalian cell is engineered with a variant GRP78 that has a mutant epitope comprising a mutation of one or more amino acid residues of the target epitope of the antibody or antigen binding fragment; and
    (b) culturing the modified mammalian cell line under conditions so that the anti-GRP78 antibody is produced in the culture supernatant.

44. The method of claim 43, further comprising (c) isolating the anti-GRP78 antibody from the culture supernatant.

45. The method of claim 43 or claim 44, wherein the antibody is a humanized antibody.

46. The method of claims 43 or claim 44, wherein the antibody is a human antibody.

47. A method of recombinant production of an antibody, the method comprising:
    (a) expressing a nucleic acid encoding an antibody in a modified mammalian cell line, wherein the antibody specifically binds a target epitope on an intracellular signaling protein that is natively expressed in the mammalian cell line and wherein the modified mammalian cell line is engineered to express a variant intracellular signaling protein that comprises a mutation of one or more amino acid residues of the target epitope; and
    (b) culturing the modified mammalian cell line under conditions so that the antibody is produced.

48. The method of claim 47, further comprising (c) isolating the antibody from the culture supernatant.

49. The method of claim 47, wherein intracellular signaling protein is a phosphatase.

50. The method of claim 47, wherein intracellular signaling protein is a kinase.