CLAIMS

1. A method of preparing a cell line adapted for efficient production of protein, comprising:

   (a) forming a plurality of cell hybrids from a starting cell population by fusing cells in the starting cell population;

   (b) sorting the cell hybrids or progeny thereof according to the density of endoplasmic reticulum and/or Golgi apparatus per cell; and

   (c) selecting and recovering cells from the sorted in step (b) that have a high density of endoplasmic reticulum and/or Golgi apparatus per cell relative to other cells in the population;

   thereby obtaining a producer cell line that supports increased production and/or secretion of recombinant protein compared with other cells in the starting population.

2. The method of claim 1, wherein the cell hybrids are formed from a single cell line.

3. The method of claim 1, wherein the cell hybrids are formed by fusing cells from an established cell line with a population of primary cells.

4. The method of claim 1, wherein the starting cell population comprises CHO cells, mouse myeloma NS0 cells, mouse myeloma SP2/0 cells, Human Embryonic Kidney (HEK) 293 cells, or Baby Hamster Kidney (BHK-21) cells.

5. The method of any preceding claim, wherein step (b) includes incubating cells in the population with a vital dye that stains endoplasmic reticulum and/or Golgi, and sorting the cells according to the amount of the vital dye associated with each cell.

6. The method of any preceding claim, wherein step (b) includes sorting the cells according to the level of a particular marker protein or glycosylation pattern produced by each cell, compared with other cells in the population.

7. The method of any preceding claim, wherein step (c) includes selecting and recovering cells from the population that have a relatively high density of endoplasmic reticulum per cell, compared with other cells in the population.

8. The method of any preceding claim, wherein step (c) includes selecting and recovering cells from the population that have a relatively high density of Golgi apparatus per cell, compared with other cells in the population.

9. A method of preparing a cell line adapted for efficient production of protein, comprising:

(a) forming a plurality of cell hybrids from a starting cell population by fusing cells in the starting cell population;

(b) expressing a fusion protein in cells in the cell hybrids or progeny thereof, wherein the fusion protein contains a fluorescent or bioluminescent peptide that generates an optical signal fused with a peptide that is processed by endoplasmic reticulum and/or Golgi apparatus; and

(c) selecting and recovering cells that express the optical signal at a higher level relative to other cells in the cell population,

thereby obtaining a producer cell line that supports increased production and/or secretion of recombinant protein compared with other cells in the starting population.

10. The method of any preceding claim, wherein cells are further selected for increased growth rate compared with the starting cell population provided in step (a).

11. The method of any preceding claim, further comprising transfecting cells from the cell population with a transgene to obtain a transfected cell population, and then selecting transfected cells from the transfected cell population that produce high levels of a protein product of the transgene, relative to other cells in the transfected cell population.

12. The method of claim 10, wherein the transfecting is performed before step (b) or after step (c).

13. A method of preparing a cell line adapted for efficient production of a protein, the method comprising:

(1) obtaining a producer cell line that has been prepared according to the method of any of claims 1 to 10;

(2) introducing a transgene encoding the intended protein into the genome of a plurality of cells of the cell line; and

(3) selecting cells transfected with the transgene that produce the protein.

14. A producer cell line that has a relatively high density of endoplasmic reticulum and/or Golgi apparatus per cell, compared with cells of a parental cell line, thereby adapting the producer cell line for efficient production of a protein,

wherein cells of the producer cell line include a transgene encoding the intended protein that is integrated into the genome of the cells;

wherein the producer cell line has been prepared from the parental cell line by the following process:

(a) forming a plurality of cell hybrids by fusing cells in the parental cell line;

(b) sorting the hybrids or progeny thereof according to the density of endoplasmic reticulum and/or Golgi apparatus per cell;

(c) selecting and recovering cells from the cells sorted in step (b) that have a relatively high density of endoplasmic reticulum and/or Golgi apparatus per cell compared with the starting cell line; and

(d) culturing the cells selected and recovered in step (c), thereby establishing the producer cell line.

15. A system for efficient protein production, comprising both the starting cell line and the producer cell line derived therefrom according to claim 14.

16. The producer cell line of claim 15, wherein the cell hybrids are formed from a single cell line.

17. The producer cell line of claim 15, wherein the cell hybrids are formed by fusing cells from the starter cell line with a population of primary cells.

18. The producer cell line of claim 15, wherein the parental cell line is a line of CHO cells, mouse myeloma NS0 cells, mouse myeloma SP2/0 cells, Human Embryonic Kidney (HEK) 293 cells, or Baby Hamster Kidney (BHK-21) cells.

19. The producer cell line or system according to any of claims 14 to 18, wherein the producer cell line contains a transgene that encodes a target protein of interest for commercial production.

20. The producer cell line or system according to claim 19, wherein cells of the producer cell line have one or more of the following features in any combination as a result of having been obtained according to said process:

the cells are aneuploid;

the cells produce at least 8 grams of the target protein per liter of culture fluid;

the cells produce 50 to 200 pg/cell/day of the target protein;

the cells contain 2 to 10-fold more endoplasmic reticulum or Golgi per cell, compared with cells of the starter cell line;

the cells produce 2 to 10-fold more of the target protein per cell, compared with cells of the starter cell line.

21. The producer cell line or system according to claim 19 or 20, wherein cells of the producer cell line have one or more of the following features in any combination as a result of having been obtained according to said process:

the cells produce 10 to 20 grams of the target protein per liter of culture fluid;

the cells produce at least 65 pg/cell/day of the target protein;

the cells contain at least 4-fold more endoplasmic reticulum or Golgi per cell, compared with cells of the starter cell line;

the cells produce at least 4-fold more of the target protein per cell, compared with cells of the starter cell line.

22. A method of producing a pharmaceutical product, comprising:

obtaining a producer cell line or system that contains a transgene encoding a target protein according to any of claims 19 to 21;

culturing cells from the producer cell line under conditions whereby the target protein is expressed from the transgene;

purifying the target protein from the cell culture; and

compounding the purified protein so as to produce the pharmaceutical product in a manner such that the product is suitable for human administration.

23. The method of claim 22, wherein the pharmaceutical product contains a target protein selected from an antibody chain, a therapeutic enzyme, a hormone, a growth factor, and a naturally occurring component of blood.

24. A hybrid cell line, comprising part or all of the genome of two or more parental cell lines, a higher concentration of endoplasmic reticulum and/or Golgi apparatus relative to any of the parental cell lines, and a capacity to produce at least eight grams of protein per liter of culture fluid from one or a combination of recombinantly inserted genes.

25. A method of producing a protein for compounding as a biopharmaceutical, the method comprising:

obtaining cells from a hybrid cell line according to claim 24, wherein the recombinantly inserted gene(s) encode part or all of the protein, and

culturing the cells under conditions whereby the protein or a portion thereof is expressed by the cells from the recombinantly inserted gene(s).