CLAIMS

1. A method of selecting a cell having increased production capacity and/or which produces increased quality of a recombinant polypeptide product, comprising:

a) contacting a population of cells with an inhibitor of a protein degradation pathway;

b) evaluating the effect of the inhibitor on the quantity of a polypeptide product or on the quality of a polypeptide product produced by one or more cells in the population of cells compared with cells of the same type that have not been contacted with the inhibitor; and

c) selecting a cell or a progeny cell thereof if it has increased production capacity and/or increased quality of the polypeptide product compared to a cell of the same type that has not been contacted with the inhibitor.

2. The method of claim 1, wherein the inhibitor is a proteasome inhibitor, ubiquitin pathway inhibitor, or an ERAD inhibitor.

3. The method of claim 1 or 2, wherein cell the polypeptide in step (b) is a recombinant protein encoded by an exogenous nucleic acid.

4. The method of any of claims 1-3, further comprising establishing a cell line from the cell selected in step (c) or a progeny cell thereof.

5. The method of any of claims 1-4, wherein the amount of polypeptide product in step (b) produced in the presence of the inhibitor is increased and/or the improved quality of the product comprises one or more of the following: an increased level, amount, or proportion of the desired product, e.g., with respect to unwanted isoforms, fragmented, or truncated forms; an increased level, amount, or proportion of properly folded product; an increased level, amount, or proportion of functional, e.g., enzymatically active, product; a decreased level, amount, or proportion of aggregated product; or a decreased level, amount, or proportion of fragmented or unwanted isoforms;

as compared to the level, amount, or quantity produced by a cell that has not been contacted by the inhibitor.

6. The method of any of claims 1-5, wherein the inhibitor is a proteasome inhibitor, optionally, wherein the proteasome inhibitor inhibits or reduces the activity of one or more of the 20S core subunit, the 19S regulatory subunit, the 11S regulatory particle, or a chaperone protein that assist proteasome assembly, e.g., Hsm3/S5b, Nas2/p27, Rpn14/PAAF1, and Nas6/gankyrin, optionally, wherein the proteasome inhibitor is selected from MG132, epoxomicin, bortezomib, ixazomib, carfilzomib, disulfiram, CEP-18770, ONX 0912, salinosporamide, LLnV, CEP1612, lactacystin, PS-341, and eponomicin.

7. The method of any of claims 1-5, wherein the inhibitor is an ERAD inhibitor, optionally, wherein the ERAD inhibitor inhibits or reduces the activity of one or more of calnexin/calreticulin, UDP-glucose-glycoprotein glucosyltransferase, ER degradation enhancing α-mannosidase-like protein (EDEM), ER mannosidase I, Sec61, CDC48p (VCP/p97), Hrd1, Doa10, Ubc6, Ubc1, Cue1, or Ubc7, optionally, wherein the inhibitor of protein degradation is eeyarestatin I.

8. The method of any of claims 1-5, wherein the inhibitor is a ubiquitin pathway inhibitor, optionally, wherein the ubiquitin pathway inhibitor inhibits or reduces the activity of one or more of: E1 ubiquitin activating enzyme, E2 ubiquitin conjugating enzyme, or E3 ubiquitin ligase.

9. The method of any of claims 1-8, further comprising contacting the cell with a second inhibitor of a protein degradation pathway, optionally, wherein the cell is contacted with a first and a second inhibitor of protein degradation, e.g., concurrently or sequentially.

10. The method of claim 9, wherein:

(i) the first inhibitor of protein degradation and second inhibitor of a protein degradation pathway are selected from MG132, epoxomicin, or eeyarestatin 1;

(ii) the first inhibitor is a proteasome inhibitor and the second inhibitor is a proteasome inhibitor;

(iii) the first inhibitor is a proteasome inhibitor and the second inhibitor is an ERAD inhibitor or an ubiquitin pathway inhibitor;

(iv) the first inhibitor is an ERAD inhibitor and the second inhibitor is an ERAD inhibitor;

(v) the first inhibitor is an ERAD inhibitor and the second inhibitor is an ubiquitin pathway inhibitor or a proteasome inhibitor;

(vi) the first inhibitor is an ubiquitin pathway inhibitor and the second inhibitor is an ubiquitin pathway inhibitor; or

(vii) the first inhibitor is an ubiquitin pathway inhibitor and the second inhibitor is an ERAD inhibitor or a proteasome inhibitor.

11. The method of any of claims 1-10, wherein the cell is contacted with a concentration of the inhibitor of protein degradation that is sufficient to reduce culture viability, by about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%, e.g., as compared to the culture viability before the culture is contacted with the inhibitor or as compared to a culture that is not contacted with the inhibitor, optionally, wherein the concentration of the inhibitor of protein degradation is a concentration at which one or more cells continue to proliferate.

12. The method of any of claims 1-11, wherein the concentration of the inhibitor of protein degradation is less than 0.5 μM MG-132; or less than 0.05 μM epoxomicin.

13. The method of any of claims 1-12, wherein the cell is contacted by, e.g., cultured in, the inhibitor of protein degradation for 24, 48, 72, 96, or more hours.

14. The method of any of claims 1-13, wherein the cell is contacted by the inhibitor of protein degradation 24, 48, 72, 96, or 168 hours prior, after, or simultaneously or concurrently a selection step.

15. The method of any one of claims 3-14, wherein the recombinant polypeptide is selected from an antibody molecule, a bispecific molecule, a blood clotting factor, an anticoagulant, a hormone, an interferon, an interleukin, and enzymes elected from Table 1 or 2.

16. The method of any of claims 1-15, wherein the cell is a mammalian cell.

17. The method of any of claims 1-16, wherein the cell is from mouse, rat, Chinese hamster, Syrian hamster, monkey, human, dog, camel, horse, ferret, or cat;.

18. The method of any of claims 1-17, wherein the cell is a CHO cell.

19. The method of any of claims 1-17, wherein the cell is a selected from HeIa, HEK293, H9, HepG2, MCF7, Jurkat, NIH3T3, PC12, PER.C6, BHK, VERO, SP2/0, NS0, YB2/0, EB66, C127, L cell, COS, e.g., COS1 and COS7, QC1-3, CHOK1, CHOK1SV, Potelligent CHOK1SV, CHO GS knockout, CHOK1SV GS-KO, CHOS, CHO DG44, CHO DXB11, and CHOZN.

20. The method of any of claims 1-20, wherein the polypeptide product in step (b) is evaluated for a parameter related to a physical or functional property, e.g., primary sequence, glycosylation, primary, secondary, tertiary, or quaternary structure, activity, degree of glycosylation, degree of aggregation, proportion or level of the expressed product having a preselected property, e.g., having a preselected monomeric, dimeric, or trimeric structure, or the level or proportion of the expressed product having a preselected structure, e.g., non-denatured or non-aggregated structure.

21. A method of making a cell line, or a population of cells, comprising:

a) selecting a cell by the method of any of claims 1-20; and

b) culturing the cell, or population of cells, to provide a cell line or population of cells.

22. The method of claim 21, further comprising introducing to the cell line or population of cells an exogenous nucleic acid that encodes a recombinant polypeptide.

23. The method of claim 22, further comprising expressing the recombinant polypeptide, from the cell line, population of cells or progeny cells thereof.