CLAIMS

~~What is claimed is:~~

~~Claim 1.~~ 1. A method of controlling the number of disulfide bonds between polypeptides of a multimeric protein produced by a bioprocess, the method comprising:

(a) contacting the polypeptides with a conditioned solution at a specific time point during the bioprocess, wherein the conditioned solution has a pH between 3.4 to 6; and wherein the conditioned solution comprises a redox reagent, wherein the redox reagent is 2-mercaptoethylamine (2-MEA);

~~wherein the conditioned solution comprises one or more predetermined solution parameters, and~~

(b) incubating the conditioned solution comprising the polypeptides for a predetermined time at a predetermined temperature~~;~~, wherein the predetermined temperature of the incubation is between 2°C and 23°C; and

wherein the incubation of the polypeptides with the conditioned solution ~~controls~~increases the ~~formation~~number of disulfide bonds formed between the polypeptides of the protein~~.~~

~~Claim 2. The method of claim 1,~~ , and wherein the ~~number of disulfide bonds between the polypeptides of the~~multimeric protein is ~~increased.~~

~~Claim 3. The method of claim 1, wherein the number of disulfide bonds between the polypeptides of the protein is decreased.~~

~~Claim 4. The method of claim 1, wherein the number of disulfide bonds between the polypeptides of the protein is maintained.~~

~~Claim 5.~~ ~~The method of claim 1, wherein the predetermined solution parameters comprise one~~an antibody or ~~more of: redox reagent identity, redox reagent concentration, pH, gas identity, dissolved gas levels, conductivity, and viable cell density.~~ antibody fragment.

~~Claim 6. The method of claim 5, wherein the redox reagent identity is 2-mercaptoethylamine (2-MEA), reduced glutathione, oxidized glutathione, 2-mercaptoethanol, dithiothreitol (DTT), cysteine, cystine, dithiobutylamine, or sodium sulfite.~~

~~Claim 7. The method of claim 6, wherein the redox reagent identity is 2-mercaptoethylamine (2-MEA).~~

~~The method of claim 6~~

~~Claim 8.~~ 2. The method of claim 1, wherein the ratio of redox reagent molarity to protein molarity is at least about 4:1, 8:1, 16:1, or 32:1.

~~Claim 9.~~ 3. The method of claim 1~~, wherein the predetermined temperature of the incubation is between about 2°C and about 23°C.~~

~~Claim 10. The method of claim 1, wherein the predetermined temperature of the incubation is between about 23°C and about 37°C~~ or ~~higher.~~

~~Claim 11.~~ ~~The method of claim 1~~2, wherein the conditioned solution comprising the polypeptides is mixed during incubation.

~~Claim 12.~~ 4. The method of ~~claim~~any one of claims 1 to 3, further comprising~~:~~

removing the polypeptides from the bioprocess at the specific time point during the bioprocess.

~~Claim 13.~~ 5. The method of claim ~~1~~24, further comprising~~:~~

returning the polypeptides to the bioprocess after incubation.

~~Claim 14.~~ 6. The method of ~~claim~~any one of claims 1 to 5, wherein the bioprocess comprises a batch, semi-continuous, or continuous bioprocess.

~~Claim 15.~~ 7. The method of ~~claim~~any one of claims 1 to 6, wherein the specific time point during the bioprocess comprises a time point after a bioreactor operation or fed batch cell culture operation in the bioprocess.

~~Claim 16.~~ 8. The method of ~~claim~~any one of claims 1 to 6, wherein the specific time point during the bioprocess comprises a time point wherein the polypeptides are in a solution comprising a plurality of cells.

~~Claim 17.~~ 9. The method of claim ~~16~~8, wherein the specific time point during the bioprocess comprises a time point wherein the polypeptides are located in a bioreactor, holding tank, or a non-bioreactor unit operation vessel comprising a plurality of cells.

~~Claim 18.~~ 10. The method of ~~claim~~any one of claims 1 to 6, wherein the specific time point during the bioprocess comprises a time point wherein the polypeptides are in a cell-free solution.

~~Claim 19.~~ 11. The method of claim ~~18~~10, wherein the specific time point during the bioprocess comprises a time point wherein the polypeptides are located in a holding tank.

~~Claim 20.~~ 12. The method of claim ~~18~~10 or 11, wherein the specific time point during the bioprocess comprises a time point during the step of viral inactivation, adjustment, chromatography, filtration, dilution, concentration, or any bioprocess step that is cell-free.

~~Claim 21.~~ 13. The method of ~~claim 18~~any one of claims 10 to 12, wherein the specific time point during the bioprocess comprises a time point during the clarification stage, clarified harvest stage, capture stage, intermediate chromatography stage, or polishing chromatography stage of the bioprocess.

~~Claim 22.~~ 14. The method of ~~claim 18~~any one of claims 10 to 13, wherein the cell-free solution comprises clarified harvest.

~~Claim 23.~~ 15. The method of ~~claim 18~~any one of claims 10 to 14, wherein the cell-free solution comprises Protein A eluate.

~~Claim 24. The method of claim 1, wherein the multimeric protein is a non-antibody protein.~~

~~Claim 25. The method of claim 1, wherein the multimeric protein is an antibody.~~

~~Claim 26.~~ 16. The method of ~~claim 1, wherein the multimeric protein is an antibody fragment.~~

~~Claim 27. The method~~any one of ~~claim 25 or 26~~claims 1 to 15, wherein the polypeptides of the multimeric protein comprise heavy chain polypeptides~~.~~

~~Claim 28. The method of claim 25 or 26, wherein the polypeptides of the multimeric protein comprise~~, light chain polypeptides~~.~~

~~Claim 29.~~ ~~The method of claim 25 or 26, wherein the polypeptides of the multimeric protein comprise~~ or heavy chain ~~polypeptides~~ and light chain polypeptides.

~~Claim 30.~~ 17. The method of ~~claim~~any one of claims 1 to 16, wherein the polypeptides are monomers or multimers of the protein.

~~Claim 31.~~ 18. A method of controlling the proportion of half antibody molecules in a solution comprising a population of antibody molecules, the method comprising:

(a) contacting the solution comprising the population of antibody molecules with a conditioned solution, wherein the conditioned solution has a pH between 3.4 to 6; and

wherein the conditioned solution comprises ~~predetermined solution parameters; and~~a redox reagent, wherein the redox reagent is 2-mercaptoethylamine (2-MEA);

(b) incubating the conditioned solution comprising the antibody molecules for a predetermined time at a predetermined temperature, wherein the predetermined temperature of the incubation is between 2°C and 23°C;

wherein the incubation of the antibody molecules with the conditioned solution ~~controls~~decreases the proportion of half antibody molecules in the conditioned antibody solution.

~~Claim 32.~~ 19. The method of ~~claim 31, wherein the predetermined solution parameters comprise redox reagent selection, redox reagent concentration, pH, gas selection, dissolved gas levels, conductivity, viable cell density, or protein concentration.~~

~~Claim 33.~~ ~~The method~~any one of ~~claim 25 or 31~~claims 1 to 18, wherein the antibody is an IgG4 antibody.

~~Claim 34.~~ 20. The method of claim ~~31~~18, wherein the antibody is an antibody fragment.

~~Claim 35.~~ 21. The method of ~~claim 26~~any one of claims 1 to 18 or ~~34~~20, wherein the antibody fragment is an IgG4 antibody fragment.

~~Claim 36.~~ 22. The method of ~~claim 31~~any one of claims 18 to 21, wherein the proportion of half antibody molecules in the conditioned antibody solution is less than 30 percent.

~~Claim 37.~~ 23. The method of ~~claim 31~~any one of claims 18 to 22, wherein the proportion of half antibody molecules in the conditioned antibody solution is less than 15 percent.

~~Claim 38.~~ 24. The method of claim ~~33~~18 or 19, wherein the antibody solution comprises natalizumab, gemtuzumab, or fresolimumab.