

## CLAIMS

1. A method for producing a composition comprising a homodimer and/or a multimer of the homodimer, wherein the homodimer comprises two monomers each comprising amino acids 21-264 of SEQ ID NO:4, the method comprising:

(a) culturing Chinese Hamster Ovary (CHO) cells that have been stably transfected with an expression vector comprising a nucleic acid sequence encoding SEQ ID NO: 4 at a growth temperature of  $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ . for 5 days;

(b) shifting the growth temperature from  $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ . to  $32.5^{\circ}\text{C} \pm 1^{\circ}\text{C}$ .; and

(c) harvesting the homodimer and/or the multimer of the homodimer from the culture media.

2. The method of claim 1, wherein the cells are grown to a density of about 10 to about 25 million cells/mL, to a density of about 10 to about 15 million cells/mL, or to a density of about 15 to about 20 million cells/mL prior to shifting the growth temperature.

3. The method of claim 1, wherein the culturing is done in ActiCHO P base culture media comprising glutamine and wherein the CHO cells are fed during culture with ActiCHO feed A and ActiCHO feed B.

4. The method of claim 1, wherein the expression vector comprising the nucleic acid sequence encoding SEQ ID NO: 4 comprises a nucleic acid sequence encoding the leader peptide of SEQ ID NO: 1.

5. The method of claim 1, wherein the expression vector results in less than 20 genomic insertions.

6. A method for producing a composition comprising a homodimer and/or a multimer of the homodimer, wherein the homodimer comprises two monomers each comprising amino acids 21-264 of SEQ ID NO:4, the method comprising:

(a) transfecting Chinese Hamster Ovary (CHO) cells with an expression vector comprising a nucleic acid encoding SEQ ID NO: 4;

(b) culturing the CHO cells from (a) in a bioreactor with ActiCHO P media at a growth temperature of 37° C.±1;

(c) feeding the cultures of (b) with Acti CHO Feed A and Acti CHO Feed B daily at a growth temperature of 37° C.±1° C. for 5 days;

(d) shifting the growth temperature from 37° C.±1° C. to 32.5° C.±1° C.; and

(e) harvesting the homodimer and/or multimer of the homodimer from the culture media, wherein >70% of the composition is present as the multimer of the homodimer, and wherein >30% of the multimers are higher order multimers.

7. The method of claim 6, wherein cell viability exceeds 85% at day 18 of culture.

8. The method of claim 6, wherein greater than 80% of the composition comprises the multimer of the homodimer.

9. A method of purifying the homodimer and/or multimer of the homodimer produced by the method of claim 1 comprising:

(a) purifying the homodimer and/or multimer of the homodimer from the culture supernatant by affinity chromatography; and

(b) polishing the homodimer and/or multimer of the homodimer by one or more of cation exchange chromatography, anion exchange chromatography, and hydrophobic interaction chromatography.

10. The method of claim 9, wherein the affinity chromatography uses a Mab Select SuRe protein A column.

11. The method of claim 9, wherein purification by affinity chromatography comprises eluting the homodimer and/or multimer of the homodimer from the affinity chromatography column using an elution buffer comprising sodium acetate and NaCl.

12. The method of claim 10, wherein the protein A column is regenerated with an NaOH buffer of at least 0.5 M.
13. The method of claim 9, wherein polishing the homodimer and/or multimer of the homodimer comprises anion exchange flow through chromatography.
14. The method of claim 13, wherein anion exchange flow through chromatography comprises using a Q Sepharose Fast Flow column.
15. The method of claim 9, wherein polishing the homodimer and/or multimer of the homodimer comprises cation exchange chromatography.
16. The method of claim 15, wherein cation exchange chromatography comprises using a POROS XS column.
17. The method of claim 15, wherein cation exchange chromatography comprises using a sodium acetate elution buffer.
18. The method of claim 17, wherein the elution buffer further comprises 36.5-38.5% of a 1 M NaCl buffer.
19. The method of claim 9, wherein polishing the homodimer and/or multimer of the homodimer comprises hydrophobic interaction chromatography.
20. The method of claim 19, wherein hydrophobic interaction chromatography comprises using a Phenyl Sepharose 6 Fast Flow High Sub Resin.
21. A method for purifying and polishing a composition comprising a homodimer and/or a multimer of the homodimer, wherein the homodimer comprises two monomers each comprising amino acids 21-264 of SEQ ID NO:4 comprising:

(a) purifying the homodimer and/or multimer of the homodimer from a culture supernatant by protein A affinity chromatography, wherein the protein A chromatography uses an alkaline-resistant medium such as the MabSelect SuRe medium, wherein purifying is performed with at least two wash cycles;

(b) polishing the homodimer and/or multimer of the homodimer by cation exchange chromatography, wherein the cation exchange chromatography uses a high-capacity, high-resolution resin such as POROS XS, and wherein the elution buffer is a sodium acetate buffer comprised of 36.5-38.5% of a 1 M NaCl buffer;

(c) polishing the homodimer and/or multimer of the homodimer by anion exchange chromatography, wherein the anion exchange chromatography uses an anion exchange medium such as the Q Sepharose Fast Flow medium; and

(d) polishing the homodimer and/or multimer of the homodimer by hydrophobic interaction chromatography (HIC), wherein the HIC medium is Phenyl Sepharose 6 Fast Flow High Sub Resin and is selected to isolate or remove a particular fraction of the multimer of the homodimer in addition to polishing.

22. The method of claim 21, wherein the final protein titer of the composition is >4 g/L.

23. The method of claim 21, wherein the composition comprises >70% multimers.

24. The method of claim 1, further comprising shifting the pH from 7.1 to 7.0 at day 5.

25. The method of claim 6, further comprising shifting the pH from 7.1 to 7.0 at day 5.

26. The method of claim 6, wherein the final protein titer is at least 7.2 g/L.

27. A method for producing a composition comprising a homodimer and/or a multimer of the homodimer, wherein the homodimer comprises two monomers each comprising amino acids 21-264 of SEQ ID NO:4, the method comprising:

(a) culturing Chinese Hamster Ovary (CHO) cells, that have been stably transfected with an expression vector comprising a nucleic acid sequence encoding SEQ ID NO: 4, at a growth

temperature of  $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ . until the CHO cells reach a cell density of about 5 to about 30 million cells/mL;

(b) shifting the growth temperature from  $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ . to  $32.5^{\circ}\text{C} \pm 1^{\circ}\text{C}$ .; and

(c) harvesting the homodimer and/or the multimer of the homodimer from the culture media.