CLAIMS

1. A method of culturing heterologous protein-secreting mammalian cells in a cell culture supernatant wherein the cell culture supernatant has a dissolved CO_2 concentration of 1 to 10%, wherein the cell culture is a continuous culture maintained at a density of from $1.4x10^6$ to $2.8x10^6$ cells/ml.

2. The method according to claim 1 wherein the CO_2 concentration is either 4.0 to 9.0% or 5.5 to 8.5%.

3. The method according to claim 1 wherein the cell culture supernatant is maintained at a temperature that is set at from 34.2°C to less than 37°C.

4. The method according to claim 3 wherein the temperature is selected from 35.1°C to 36.9°C, 34.2°C to 36.0°C, and 35.6°C to less than 37°C.

5. The method according to claim 1 or 3 wherein the cell culture supernatant is maintained at a pH that is set at from greater than 7.10 to 7.25.

6. The method according to any preceding claim wherein the cell culture supernatant is buffered with bicarbonate.

7. The method according to any preceding claim wherein the supernatant is sparged with air.

8. The method according to any preceding claim wherein the heterologous protein is a blood protein.

9. The method according to claim 1 wherein the heterologous protein is Factor VIII.

10. The method according to claim 9 wherein the Factor VIII is co-expressed with von Willebrand Factor.

11. The method according to any preceding claim wherein the concentration of Cu^{2+} in the cell culture supernatant is at least 5, 7, 10, 15 or 25 ppb.

12. The method according to claim 1 wherein the heterologous protein is ADAMTS-13, furin or Factor VII.

13. The method according to any preceding claim wherein the mammalian cell is a rodent cell, such as a CHO cell or a BHK cell.

14. The method according to any preceding claim wherein the continuous culture is a chemostat or turbidostat culture.