[0084] In a ninth aspect, the present invention provides a cell culture supernatant comprising recombinant Von Willebrand Factor (rVWF), wherein the supernatant contains at least 2 μg rA13 per mL. In a specific embodiment, the supernatant contains at least 3 μg rA13 per mL. In another specific embodiment, the supernatant contains at least 4 μg rA13 per mL. In another specific embodiment, the supernatant contains at least 5 μg rA13 per mL. In another specific embodiment, the supernatant contains at least 6 μg rA13 per mL. In yet another specific embodiment of the supernatants provided above, the supernatant is prepared according to a method provided herein.

[0085] In a tenth aspect, the present invention provides a recombinant ADAMTS13 (rA13) composition prepared by a method according to any one of the methods described above.

[0086] In one embodiment of the compositions provided above, the composition is formulated for pharmaceutical administration. In a specific embodiment, the composition is formulated for intravenous administration.

[0086a] In an eleventh aspect, the present invention provides a method for producing a recombinant Von Willebrand Factor (rVWF) composition, the method comprising the steps of:

(a) providing a basal cell culture media;

(b) supplementing the basal cell culture media with copper to provide a final copper concentration between 2.4 μg/L and 20 μg/L;

(c) providing one or more cells comprising a nucleic acid encoding a rVWF protein;

(d) culturing the one or more cells in the copper supplemented cell culture media such that rVWF is expressed and excreted from the cells into a culture supernatant, wherein an $NH4^+$ content of the cell culture supernatant is maintained at a concentration below 4 mM wherein the cell density is maintained at less than 2.5×10^6 cells per mL during the step of culturing the one or more cells; and

(e) recovering at least a portion of the culture supernatant,

wherein the recovered supernatant has a rVWF specific ristocetin cofactor activity of at least 30 mU/μg rVWF.

BRIEF DESCRIPTION OF DRAWINGS

[0087] Figure 1. (1A) Low resolution (1 %) agarose gel electrophoresis of rVWF expressed in mammalian cell culture in the presence of low (1.0 μg/L) and high (4.3 μg/L) copper concentration, as described in Example 2. Note that culture Day 3 is equivalent to batch day 1 of Table 7 and Table **8**. (**IB**) The relative amounts of VWF multimers having 1 to 10 dimers (band number 1) and more than 10 dimers (band number 2), as indicated by the bands defined in Figure 1A, was quantitated by densitometric analysis.

[0088] Figure 2. (2A) Interval plot of the average rVWF specific activity present in rVWF cell culture supernatants grown at high and low cell densities in the presence of high or low levels of copper. (**2B**) Interval plot of the average NH_4^+ concentration found in rVWF cell culture supernatants grown at high and low cell densities in the presence of high or low levels of copper.

[0089] Figure 3. Supernatants from cell cultures expressing recombinant ADAMTS13 in the presence of increasing levels of copper were investigated by SDS-PAGE analysis. rA13 was visualized after SDS-PAGE by (**3A**) silver staining and (**3B**) anti-A13 western blotting.

WHAT IS CLAIMED IS:

1. A method for producing a recombinant Von Willebrand Factor (rVWF) composition, the method comprising the steps of:

(a) providing a basal cell culture media;

(b) supplementing the basal cell culture media with copper to provide a final copper concentration between 2.4 μg/L and 20 μg/L;

(c) providing one or more cells comprising a nucleic acid encoding a rVWF protein;

(d) culturing the one or more cells in the copper supplemented cell culture media such that rVWF is expressed and excreted from the cells into a culture supernatant, wherein an $NH4^+$ content of the cell culture supernatant is maintained at a concentration below 4 mM wherein the cell density is maintained at less than 2.5×10^6 cells per mL during the step of culturing the one or more cells; and

(e) recovering at least a portion of the culture supernatant,

wherein the recovered supernatant has a rVWF specific ristocetin cofactor activity of at least 30 mU/μg rVWF.

2. The method of claim 1, further comprising the step of supplementing the basal cell culture media with a hydrolysate prior to culturing the one or more cells.

3. The method of claim 2, wherein the hydrolysate is a plant hydrolysate.

4. The method of claim 3, wherein the hydrolysate is a soy hydrolysate.

5. The method according to any one of claims 1 to 4, wherein the basal cell culture media is an animal protein free culture media.

6. The method according to any one of claims 1 to 4, wherein the basal cell culture media is a protein free culture media.

7. The method according to any one of claims 1 to 6, wherein the basal cell culture media is a chemically defined culture media.

29. The method according to any one of claims 1 to 27, wherein at least 20% of the rVWF in the supernatant is present in a high molecular weight VWF multimer of more than 10 dimers.

30. The method according to any one of claims 1 to 27, wherein at least 30% of the rVWF in the supernatant is present in a high molecular weight VWF multimer of more than 10 dimers.

31. The method according to any one of claims 1 to 30, wherein the supernatant contains high molecular weight VWF multimers of 14 to 22 dimers.

32. The method according to any one of claims 1 to 31, wherein rVWF is co-expressed with recombinant Factor VIII (rFVIII).

33. The method of claim 32, further comprising a step of purifying rVWF away from at least 50% of the rFVIII present in the recovered supernatant.

34. The method of claim 33, wherein the ratio of rVWF to rFVIII after the purification step is at least 10:1.

35. The method according to any one of claims 1 to 34, wherein the method further comprises a rVWF enrichment step.

36. A cell culture supernatant comprising recombinant Von Willebrand Factor (rVWF), wherein the supernatant is prepared by a method according to any one of the preceding claims.

37. A recombinant Von Willebrand Factor (rVWF) composition prepared by a method according to any one of claims 1 to 35.

38. The composition of claim 37, wherein the composition further comprises recombinant Factor VIII (rFVIII).

39. The composition of claim 38, wherein the ratio of rVWF to rFVIII is at least 10:1.

40. The composition of claim 38 or 39, wherein the composition is formulated for pharmaceutical administration.

41. The composition according to any one of claims 38 to 40, wherein the composition is formulated for intravenous administration.