previous observations. Reduction of FVIII binding activity in von Willebrand Disease (VWD), due to either reduced VWF protein levels or lowered FVIII binding affinity, results in reduced steady-state levels of endogenous FVIII (summarized in Castaman *et al.*, Disorders of Hemostasis 88(1):94-108 (2003), and improving survival of VWF has been proposed as a viable strategy for improving FVIII stability (Denis et al., Thromb Haemost. 2008 Feb;99(2):271-8; Turecek et al., Blood, 2006, 108(11): Abstract 1002). Among severe Hemophilia A patients, a correlation between pre-infusion VWF levels and the half-life of infused FVIII has been demonstrated by Fijnvandraat and colleagues (Fijnvandraat, et al., Br J Haematol. 1995 Oct;91(2):474-6). In that study, patients with 200-300% of average VWF levels were seen to have a FVIII half-life of 15-29 hours compared to a mean of 12.5 hours in patients with normal VWF levels. In another study, patients with blood group O were demonstrated to have significantly lower VWF levels and shorter FVIII half-lives (15.3 hours) compared with those with blood group A (19.7 hours) (Vlot, et al. Thromb Haemost. 2000 Jan;83(1):65-9). Chemically modified VWF has been shown to prolong survival of rFVIII (Turecek et al., J. Thromb. Haemost. 2007 Jul 9; 5(2) abstract available at: http/www.blackwellpublishing.com/isth2007/abstract.asp?id=64898). As such, co-administration of rVWF and rFVIII is a viable strategy for the treatment of coagulation diseases such as von Willebrand Disease and Hemophilia A.

SUMMARY

[0005] Accordingly, the present disclosure provides methods and combinations for treating coagulation disease by administering recombinant von Willebrand Factor (rVWF) alone or in combination with recombinant Factor VIII (rFVIII) to a subject in need thereof, with the result that the *in-vivo* half-life of Factor VIII is increased.

[0006] In one aspect, the present disclosure provides a use of a recombinant Von Willebrand Factor (rVWF) in the manufacture of a medicament for treating Von Willebrand Disease or Hemophilia A, wherein the rVWF is a high molecular weight VWF multimer composition comprising at least 40% VWF decamers or higher order multimers. In another aspect, the present disclosure relates to a use of a composition comprising a rWVF in the manufacture of a medicament for treating Von Willebrand Disease or Hemophilia A. In an embodiment, the present disclosure relates to a method for treating Von Willebrand Disease or Hemophilia A in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF) such that Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein the rVWF is a high molecular weight VWF multimer composition comprising at

least 20% VWF decamers or higher order multimers, and wherein the rVWF has a higher specific activity than plasma derived Von Willebrand Factor.

[0007] In further embodiments and in accordance with the above, methods of the disclosure include co-administering to the subject recombinant Von Willebrand Factor (rVWF) and recombinant Factor VIII (rFVIII).

[0008] In further embodiments and in accordance with any of the above, the rVWF and rFVIII are administered together in a single composition.

[0009] In further embodiments and in accordance with any of the above, the subject is administered between 1.0 IU/kg VWF:RCo and 150 IU/kg VWF:RCo per dose.

[0010] In further embodiments and in accordance with any of the above, the subject is administered between 2 IU/kg VWF:RCo and 50 IU/kg VWF:RCo per dose.

[0011] In further embodiments and in accordance with any of the above, the subject is administered between 5 IU/kg VWF:RCo and 40 IU/kg VWF:RCo per dose.

[0012] In further embodiments and in accordance with any of the above, the subject is administered between 10 IU/kg VWF:RCo and 20 IU/kg VWF:RCo per dose.

[0013] In further embodiments and in accordance with any of the above, the rVWF used in methods of the disclosure is matured in vitro by treatment with Furin.

[0014] In further embodiments and in accordance with any of the above, the rVWF is produced through expression in a Chinese Hamster Ovary (CHO cell culture).

[0015] In further embodiments and in accordance with any of the above, the rFVIII and rVWF are produced through expression in the same cell culture.

[0016] In further embodiments, and in accordance with any of the above, the subject is administered rVWF no more than once every other day.

[0017] In further embodiments and in accordance with any of the above, the subject is administered rVWF no more than twice a week.

[0018] In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition maintains the at least 20% VWF decamers or higher order multimers for at least 3 hours post-administration.

[0019] In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended by about 5 hours.

[0020] In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 12 hours.

[0021] In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 24 hours.

[0022] In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 36 hours.

[0023] In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 48 hours.

[0024] In further embodiments and in accordance with any of the above, wherein the Factor VIII half-life is extended for at least 72 hours.

[0025] In further embodiments and in accordance with any of the above, the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 2:1 and 1:4.

[0026] In further embodiments and in accordance with any of the above, the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 3:2 and 1:3.

[0027] In further embodiments and in accordance with any of the above, the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 1:1 and 1:2.

[0028] In further embodiments and in accordance with any of the above, 23 the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is about 3:4.

[0029] In further embodiments and in accordance with any of the above, the rVWF has a specific activity of about 20-150 mU/μg.

[0030] In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 30% VWF decamers or higher order multimers.

[0031] In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 40% VWF decamers or higher order multimers.

[0032] In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 50% VWF decamers or higher order multimers.

[0033] In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 60% VWF decamers or higher order multimers.

[0034] In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 70% VWF decamers or higher order multimers.

[0035] In further embodiments and in accordance with any of the above, the present disclosure provides a method for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF) such that Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein: (a) the rVWF has a higher specific activity than plasma derived Von Willebrand Factor, wherein the specific activity of

rVWF is about 20-150 mU/μg; and (b) the FVIII half-life is at least 1.5 times higher as compared to FVIII half-life in a subject administered plasma derived Von Willebrand Factor.

[0036] In further embodiments and in accordance with any of the above, the present disclosure provides a method for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF) such that Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein: (a) the rVWF is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers, (b) the rVWF has a higher specific activity than plasma derived Von Willebrand Factor, wherein the specific activity of rVWF is at least about 20-150 mU/μg; and (c) the FVIII half-life is at least 1.5 times higher as compared to FVIII half-life in a subject administered plasma derived Von Willebrand Factor.

[0037] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24 hours post-administration of the rVWF is at least 90% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0038] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24 hours post-administration is at least 100% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0039] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 36 hours post-administration is at least 80% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0040] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 48 hours post-administration is at least 50% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0041] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 6 hours post-administration.

[0042] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 12 hours post-administration.

[0043] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 18 hours post-administration.

[0044] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 24 hours post-administration.

[0045] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 36 hours post-administration.

[0046] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 48 hours post-administration.

[0047] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 72 hours post-administration.

[0048] In further embodiments and in accordance with any of the above, the present disclosure provides a method for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF).

[0049] In further embodiments and in accordance with any of the above, the method comprises co-administering to the subject recombinant Factor VIII (rFVIII) and recombinant Von Willebrand Factor (rVWF).

[0050] In further embodiments and in accordance with any of the above, the rFVIII and rVWF are administered together in a single composition.

[0051] In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 2:1 and 1:4.

[0052] In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 3:2 and 1:3.

[0053] In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 1:1 and 1:2.

[0054] In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is about 3:4.

[0055] In further embodiments and in accordance with any of the above, the rVWF is matured *in vitro* by treatment with Furin.

[0056] In further embodiments and in accordance with any of the above, the rVWF is expressed in mammalian cell culture.

[0057] In further embodiments and in accordance with any of the above, the rFVIII is expressed in mammalian cell culture.

WHAT IS CLAIMED IS:

1. Use of a recombinant Von Willebrand Factor (rVWF) in the manufacture of a medicament for treating Von Willebrand Disease or Hemophilia A, wherein the rVWF is a high molecular weight VWF multimer composition comprising at least 40% VWF decamers or higher order multimers.

2. The use according to claim 1, wherein the rVWF is matured in vitro by treatment with Furin.

3. The use according to claims 1 or 2, wherein the rVWF has a specific activity of about 20-150 mU/μg, about 30 to 120 mU/μg.

4. The use according to any one of claims 1 to 3, wherein the high molecular weight VWF multimer composition comprises at least 50% VWF decamers or higher order multimers, more preferably wherein the high molecular weight VWF multimer composition comprises at least 60% VWF decamers or higher order multimers, most preferably wherein the high molecular weight VWF multimer composition comprises at least 70% VWF decamers or higher order multimers.

5. The use according to any one of claims 1 to 4, wherein the subject is to be administered between 1.0 IU/kg VWF:RCo and 150 IU/kg VWF:RCo per dose, preferably wherein the subject is to be administered between 2 IU/kg VWF:RCo and 50 IU/kg VWF:RCo per dose, more preferred wherein the subject is to be administered between 5 IU/kg VWF:RCo and 40 IU/kg VWF:RCo per dose, very preferred wherein the subject is to be administered between 10 IU/kg VWF:RCo and 20 IU/kg VWF:RCo per dose.

6. The use according to any one of claims 1 to 5, wherein the rVWF is to be administered no more than once daily, no more than once every other day, no more than once every third day, no more than once every fourth day, no more than once every fifth day, no more than twice a week, no more than once a week, no more than once every two weeks, or no more than once a month.

7. The use according to any one of claims 1 to 6, wherein the rVWF is to be administered in multiple administrations.

8. The use according to any one of claims 1 to 7, for treating Von Willebrand Disease Type 3.

9. The use according to any one of claims 1 to 7, wherein the rVWF is to be co-administered with a Factor VIII (FVIII).

10. The use according to claim 9, wherein the FVIII is plasma derived FVIII.

11. The use according to claim 9, wherein the FVIII is recombinant FVIII.

12. The use according to any one of claims 9 to 11, wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) to be administered is between 2:1 and 1:4, preferably wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) to be administered is between 3:2 and 1:3, more preferably wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) to be administered is between 1:1 and 1:2, most preferably wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) to be administered is about 3:4.

13. The use according to any one of claims 9 to 12, wherein the rVWF is produced through expression in a Chinese Hamster Ovary (CHO cell culture), preferably wherein the rFVIII and rVWF are produced through expression in the same cell culture.

14. The use according to any one of claims 9 to 13, wherein the rVWF and rFVIII are to be administered together in a single composition.

15. The use according to any one of claims 9 to 14, for treating Von Willebrand Disease Type 3.

16. Use of a composition comprising a rWVF in the manufacture of a medicament for treating Von Willebrand Disease or Hemophilia A.

17. The use according to claim 16, wherein the composition further comprises FVIII.

18. The use according to claim 17, wherein the FVIII is plasma derived FVIII.

19. The use according to claim 17, wherein the FVIII is recombinant FVIII.

20. The use according to any one of claims 16 to 19, wherein the rVWF is produced through expression in a Chinese Hamster Ovary (CHO cell culture), preferably wherein the rFVIII and rVWF are produced through expression in the same cell culture.

21. The use according to any one of claims 16 to 20, for treating Von Willebrand Disease Type 3.