stimulation by agonists such as thrombin and histamine.

[0004] That FVIII pharmacokinetics are a function of VWF levels is supported by several 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.

BRIEF SUMMARY OF THE INVENTION

[0005] Accordingly, the present disclosure~~invention~~ 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.

[0005a] In one aspect, there is provided the use of a recombinant Von Willebrand Factor (rVWF) in the manufacture of a medicament for for treating Von Willebrand Disease or Hemophilia A in a subject in need thereof: wherein the recombinant Von Willebrand Factor (rVWF) has an extended Factor VIII half-life as compared to plasma derived Von Willebrand Factor when administered in said subject, 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.

[0005b] In another aspect, there is provided the use of a recombinant Von Willebrand Factor (rVWF) in the manufacture of a medicament for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof: wherein said recombinant Von Willebrand Factor (rVWF) has an extended Factor VIII half-life as compared to plasma derived Von Willebrand Factor when administered in said subject, and 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 of plasma derived Von Willebrand Factor in said subject.

[0005c] In another aspect, there is provided the use of a recombinant Von Willebrand Factor (rVWF) in the manufacture of a medicament for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof: wherein said recombinant Von Willebrand Factor (rVWF) has an extended Factor VIII half-life as compared to plasma derived Von Willebrand Factor when administered in said subject, 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 of plasma derived Von Willebrand Factor when administered in said subject.

[0006] ~~In one aspect, t~~The present disclosure also~~invention~~ provides 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, the methods may~~of the invention~~ 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 the disclosed methods~~ of the invention~~ 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 aspects 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 aspects and i~~In accordance with any of the above, the present disclosure~~invention~~ 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 aspects and i~~In accordance with any of the above, the present disclosure~~invention~~ 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 aspects and i~~In accordance with any of the above, the present disclosure~~invention~~ 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.