SUMMARY

[0009] The disclosure includes a method for treating, ameliorating, and/or preventing a vaso-occlusive crisis (VOC) in a subject suffering from sickle cell disease (SCD), wherein the method comprises administering to the subject in need thereof a therapeutically effective amount of a composition comprising ADAMTS13.

[0010] The disclosure includes a method for treating, ameliorating, and/or preventing a lung injury in a subject suffering from acute lung injury (ALI) and/or acute respiratory distress syndrome (ARDS), wherein the method comprises administering to the subject in need thereof a therapeutically effective amount of a composition comprising ADAMTS13.

[0011] The disclosure includes uses of ADAMTS13 and/or compositions comprising ADAMTS13 for the preparation of medicaments. Other related examples are also provided in the disclosure.

[0012] In one aspect, the present disclosure refers to use of A Disintegrin And Metalloproteinase with Thrombospondin type 1 motif, member-13 (ADAMTS13) in the preparation of a medicament for treating or preventing a vaso-occlusive crisis in a subject suffering from sickle cell disease. The disclosure provides a method for treating, ameliorating, and/or preventing a VOC in a subject suffering from SCD, the method comprising administering to the subject in need thereof a therapeutically effective amount of a composition comprising ADAMTS13. In some examples, the subject is treated after symptoms of a VOC are present. In some examples, the subject is treated before symptoms of a VOC crisis are present. In some examples, treating reduces at least one of inflammation, vasoconstriction, or platelet aggregation, or a combination of any thereof. In some examples, treating results in at least one of improved survival, improved lung function, or reduced organ damage, reduced pulmonary vascular leakage, or a combination of any thereof. In some examples, treating reduces and/or prevents at least one of impaired blood flow (e.g., ischemia), blood coagulation, vascular inflammation, thrombosis, ischemic cell damage, or organ damage, or a combination of any thereof. In some examples, treating reduces and/or prevents pain or severity of the pain. In some examples, treating reduces the frequency of occurrence of VOC and/or duration of VOC episodes. In certain examples, administration of ADAMTS13 results in reduced expression, level, and/or activation of at least one of VCAM-1, ICAM-1, P- NF-*k*B / NF-*k*B ratio, ET-1, TXAS, and HO-1 in an organ. In some examples, the comparison is to a control subject. In some examples, the comparison is to measurements taken prior to treatment.

[0013] In certain examples, organs include, but are not limited to, lung, liver, pancreas, skin, retina, prostate, ovary, lymph node, adrenal gland, kidney, heart, gallbladder or GI track. In some examples, organ tissue includes, but is not limited to the lungs, liver,

spleen, and/or kidneys. In certain examples, the organ is a lung. In certain examples, the organ is a kidney.

[0014] In certain examples, administration of ADAMTS13 results in an increase of at least one of Hct, Hb, MCV, and MCH levels in the blood and/or a reduction in at least one of CHCM, HDW, LDH, and neutrophil numbers in the blood as compared to control.

[0015] In some examples of the disclosure, the therapeutically effective amount of ADAMTS13 for treating, ameliorating, or preventing a VOC in a subject suffering from SCD is from about 20 to about 6,000 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 40 to about 4,000 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 100 to about 3,000 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 50 to about 500 international units per kilogram body weight.

[0016] In particular examples, the dosage or therapeutically effective amount for treating, ameliorating, or preventing a VOC in a subject suffering from SCD is from about 10 to about 500 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 50 to about 450 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 40 to about 150 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 100 to about 500 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 100 to about 400 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 100 to about 300 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 300 to about 500 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 200 to about 300 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, or about 500 international units per kilogram body weight.

[0017] In further examples, the dosage or therapeutically effective amount for treating, ameliorating, or preventing a VOC in a subject suffering from SCD is from about 50 to about 1,000 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 100 to about 900 international units per

kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 200 to about 800 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 300 to about 700 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 400 to about 600 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is about 500 international units per kilogram body weight.

[0018] In some examples, the composition comprising ADAMTS13, for treating, ameliorating, or preventing a VOC in a subject suffering from SCD, is administered in a single bolus injection, monthly, every two weeks, weekly, twice a week, daily, every 12 hours, every eight hours, every six hours, every four hours, or every two hours. In some examples, the composition comprising ADAMTS13 is administered intravenously or subcutaneously. In some examples, the composition comprising ADAMTS13 is administered intravenously. In some examples, the composition comprising ADAMTS13 is administered subcutaneously.

[0019] In some examples of the disclosure, the therapeutically effective amount of the composition comprising ADAMTS13 is administered to the subject within 48 hours after the onset of the VOC. In some examples, the therapeutically effective amount of the composition comprising ADAMTS13 is administered to the subject within 24 hours after the onset of the VOC. In some examples, the therapeutically effective amount of the composition comprising ADAMTS13 is administered to the subject within 12 hours after the onset of the VOC. In some examples, the therapeutically effective amount of the composition comprising ADAMTS13 is administered to the subject within 6 hours after the onset of the VOC.

[0020] In some examples of the disclosure, the therapeutically effective amount of the composition comprising ADAMTS13 for preventing the VOC is sufficient to maintain an effective level of ADAMTS13 activity in the subject. In some examples, the therapeutically effective amount of the composition comprising ADAMTS13 for preventing the VOC is administered monthly, biweekly, weekly, or twice a week to prevent a VOC. In some examples the administering is subcutaneous. In some examples, the administering is intravenous.

[0021] The disclosure includes the use of a composition comprising ADAMTS13 for treating or preventing a VOC in a subject suffering from SCD. In some examples, the

disclosure includes a composition comprising ADAMTS13 for use as a medicament for the treatment or prevention of a VOC in a subject suffering from SCD.

[0022] In certain examples, the methods of treating or preventing VOC comprises (i) administering ADAMTS13 and (ii) evaluating whether a parameter or symptom has changed, wherein the parameter is selected from the group consisting of inflammation, vasoconstriction, platelet aggregation, lung function, organ (e.g., lung or kidney) damage, pulmonary vascular leakage, blood flow, blood coagulation, vascular inflammation, thrombosis, ischemic cell damage, presence of pain, severity of pain, frequency of occurrence of VOC, duration of VOC episodes, VCAM-1, ICAM-1, P- NF-*k*B / NF-*k*B ratio, ET-1, TXAS, HO-1, Hct, Hb, MCV, HDW, reticulocyte numbers, and neutrophil numbers.

[0023] The disclosure also provides a method for treating, ameliorating, and/or preventing lung injury in a subject suffering from or at risk of suffering from ALI and/or ARDS, the method comprising administering to the subject in need thereof a therapeutically effective amount of a composition comprising ADAMTS13. In some examples, the subject suffers from a condition or a combination of the conditions selected from the group consisting of inflammatory pulmonary edema, inflammatory pulmonary infiltrates, impaired oxygenation, and hypoxemia. In some examples, treating results in at least one of improved survival, improved lung function, or reduced organ damage, reduced pulmonary vascular leakage, or a combination of any thereof. In some examples, treating reduces at least one of inflammation, vasoconstriction, or platelet aggregation, or a combination of any thereof. In some examples, treating reduces and/or prevents at least one of impaired blood flow (e.g., ischemia), blood coagulation, vascular inflammation, thrombosis, ischemic cell damage, or organ damage, or a combination of any thereof. In some examples, treating reduces and/or prevents pain or severity of the pain. In some examples, treating reduces the frequency of occurrence or ALI and/or ARDS and/or duration of ALI and/or ARDS episodes. In certain examples, administration of ADAMTS13 results in reduced expression, level, and/or activation of at least one of VCAM-1, ICAM-1, P- NF-*k*B / NF-*k*B ratio, ET-1, TXAS, and HO-1 in an organ. In some examples, the comparison is to a control subject. In some examples, the comparison is to measurements taken prior to treatment.

[0024] In certain examples, organs include, but are not limited to, lung, liver, pancreas, skin, retina, prostate, ovary, lymph node, adrenal gland, kidney, heart, gallbladder or GI track. In some examples, organ tissue includes, but is not limited to the lungs, liver, spleen, and/or kidneys. In certain examples, the organ is a lung. In certain examples, the organ is a kidney.

[0025] In certain examples, administration of ADAMTS13 results in a reduction in neutrophil numbers in the blood as compared to control.

[0026] In some examples of the disclosure, the therapeutically effective amount of ADAMTS13 for treating, ameliorating, or preventing lung injury in a subject suffering from or at risk of suffering from ALI and/or ARDS is from about 20 to about 6,000 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 40 to about 4,000 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 100 to about 3,000 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 50 to about 500 international units per kilogram body weight.

[0027] In particular examples, the dosage or therapeutically effective amount for treating, ameliorating, or preventing lung injury in a subject suffering from or at risk of suffering from ALI and/or ARDS is from about 10 to about 500 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 50 to about 450 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 40 to about 150 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 100 to about 500 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 100 to about 400 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 100 to about 300 international units per kilogram body weight. In some examples, the therapeutically effective amount is from about 300 to about 500 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 200 to about 300 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, or about 500 international units per kilogram body weight.

[0028] In further examples, the dosage or therapeutically effective amount for treating, ameliorating, or preventing lung injury in a subject suffering from or at risk of suffering from ALI and/or ARDS is from about 50 to about 1,000 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 100 to about 900 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 200 to about 800 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is from about 300 to about 700 international units per kilogram body weight. In some examples,

the dosage or therapeutically effective amount is from about 400 to about 600 international units per kilogram body weight. In some examples, the dosage or therapeutically effective amount is about 500 international units per kilogram body weight.

[0029] In some examples, the therapeutically effective amount of the composition comprising ADAMTS13, for treating, ameliorating, and/or preventing lung injury in a subject suffering from or at risk of suffering from ALI and/or ARDS, is administered to the subject within 48 hours after the detection of inflammatory pulmonary edema, inflammatory pulmonary infiltrates, impaired oxygenation, or hypoxemia. In some examples, the therapeutically effective amount of the composition comprising ADAMTS13 is administered to the subject within 24 hours after the detection of inflammatory pulmonary edema, inflammatory pulmonary infiltrates, impaired oxygenation, or hypoxemia. In some examples, the therapeutically effective amount of the composition comprising ADAMTS13 is administered to the subject within 12 hours after the detection of inflammatory pulmonary edema, inflammatory pulmonary infiltrates, impaired oxygenation, or hypoxemia. In some examples, the therapeutically effective amount of the composition comprising ADAMTS13 is administered to the subject within 6 hours after the detection of inflammatory pulmonary edema, inflammatory pulmonary infiltrates, impaired oxygenation, or hypoxemia.

[0030] In some examples, the composition comprising ADAMTS13 is administered in a single bolus injection, monthly, every two weeks, weekly, twice a week, daily, every 12 hours, every eight hours, every six hours, every four hours, or every two hours. In some examples, the composition comprising ADAMTS13 is administered intravenously or subcutaneously. In some examples, the composition comprising ADAMTS13 is administered intravenously. In some examples, the composition comprising ADAMTS13 is administered subcutaneously.

[0031] In various examples of the disclosure, ADAMTS13 is recombinant ADAMTS13. In some examples, ADAMTS13 is plasma derived.

[0032] In various examples of the disclosure, the subject is a mammal. In some examples the subject is a human.

[0033] In some examples, the composition is in a stable aqueous solution ready for administration.

[0034] In some examples, the therapeutically effective amount of the composition comprising ADAMTS13 for treating, ameliorating, and/or preventing lung injury is sufficient to maintain an effective circulating level of ADAMTS13 activity in the subject.

[0035] The disclosure includes the use of a composition comprising ADAMTS13 for treating, ameliorating and/or preventing lung injury in a subject suffering from or at risk of suffering from ALI and/or ARDS. In some examples, the subject is suffering from ALI. In some examples, the subject is suffering from ARDS.

[0036] The disclosure also includes a composition comprising ADAMTS13 for use as a medicament for the treatment, amelioration, or prevention of a lung injury in a subject suffering from or at risk of suffering from ALI and/or ARDS.

[0037] In certain examples, the methods of treating or preventing ALI/ARDS comprises (i) administering ADAMTS13 and (ii) evaluating whether a parameter or symptom has changed, wherein the parameter is selected from the group consisting of inflammation, vasoconstriction, platelet aggregation, lung function, organ (e.g., lung or kidney) damage, pulmonary vascular leakage, blood flow, blood coagulation, vascular inflammation, thrombosis, ischemic cell damage, frequency of occurrence of ALI/ARDS, duration of ALI/ARDS episodes, VCAM-1, ICAM-1, P- NF-*k*B / NF-*k*B ratio, ET-1, TXAS, HO-1, Hct, Hb, MCV, HDW, reticulocyte numbers, and neutrophil numbers.

[0038] The foregoing summary is not intended to define every aspect of the invention, and additional aspects are described in other sections, such as the following detailed description. The entire document is intended to be related as a unified disclosure, and it should be understood that all combinations of features described herein are contemplated, even if the combination of features are not found together in the same sentence, or paragraph, or section of this document. Other features and advantages of the invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, because various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DESCRIPTION OF THE FIGURES

[0039] Figure 1 is a graph showing that ADAMTS13 protects sickle cell mice (SCD) from death related to a severe acute VOC. Mice (n=6) were treated with rADAMTS13

CLAIMS

WHAT IS CLAIMED IS:

1. Use of A Disintegrin And Metalloproteinase with Thrombospondin type 1 motif, member-13 (ADAMTS13) in the preparation of a medicament for treating or preventing a vaso-occlusive crisis in a subject suffering from sickle cell disease.

2. The use according to claim 1, wherein the medicament comprises the ADAMTS13 in an amount of:

- from about 10 IU/kg to about 500 IU/kg of the subject's body weight; or
- from about 40 IU/kg to about 150 IU/kg of the subject's body weight.

3. The use according to claim 1 or claim 2, wherein the medicament comprising the ADAMTS13 is for administration:

- after symptoms of the vaso-occlusive crisis are present; or
- before symptoms of the vaso-occlusive crisis are present; or
- within 48 hours after the onset of the vaso-occlusive crisis; or
- in a single bolus injection, monthly, every two weeks, weekly, twice a week, every other day, daily, every 12 hours, every eight hours, every six hours, every four hours, or every two hours.

4. The use according to any one of claims 1-3, wherein the medicament comprising ADAMTS13 is for administration intravenously or subcutaneously.

5. The use according to any one of claims 1-4, wherein the medicament is in a stable aqueous solution ready for administration.

6. The use according to any one of claims 1-5, wherein the ADAMTS13 reduces at least one of inflammation, vasoconstriction, platelet aggregation, or a combination of any thereof as compared to control or without treatment.

7. The use according to any one of claims 1-6, wherein the ADAMTS13 reduces the frequency of occurrence of VOC and/or duration of VOC episodes as compared to control or without treatment.

8. The use according to any one of claims 1-7, wherein the ADAMTS13 results in at least one of improved survival, improved lung function, reduced organ damage, reduced pulmonary vascular leakage, or a combination of any thereof as compared to control or without treatment.

9. The use according to any one of claims 1-7, wherein the ADAMTS13 reduces at least one of inflammation, vasoconstriction, platelet aggregation, or a combination of any thereof as compared to control or without treatment.

10. The use according to any one of claims 1-7, wherein the ADAMTS13 reduces and/or prevents at least one of impaired blood flow, blood coagulation, vascular inflammation, thrombosis, ischemic cell damage, organ damage, or a combination of any thereof as compared to control or without treatment.

11. The use according to any one of claims 1-7, wherein the ADAMTS13 reduces and/or prevents pain or severity of the pain as compared to control or without treatment.

12. The use according to any one of claims 1-7, wherein the ADAMTS13 reduces expression, level, and/or activation of at least one of VCAM-1, ICAM-1, P- NF-*k*B, NF-*k*B, ET-1, TXAS, and HO-1 in an organ as compared to control or without treatment.

13. The use according to any one of claims 1-7, wherein the ADAMTS13 increases the level of at least one of Hct, Hb, MCV, and MCH in the blood as compared to control or without treatment.

14. The use according to any one of claims 1-7, wherein the ADAMTS13 reduced the level of at least one of CHCM, HDW, LDH, and neutrophil numbers in the blood as compared to control or without treatment.

15. The use according to any one of claims 1-14, wherein the ADAMTS13 is recombinant ADAMTS13.

16. The use according to any one of claims 1-14, wherein the ADAMTS13 is plasma derived.

17. The use according to any one of claims 1-16, wherein the subject is a human.