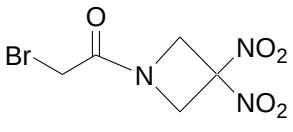
[0009] However, to recapitulate from above, ABDNAZ drug substance, despite many advantageous properties, is subject to detonation by application of shock or impact which creates potential safety issues when making, transporting, storing, and formulating the drug substance for use in therapy. Accordingly, there remains a need to create a consistently non-explosive form of ABDNAZ to enable its safe storage, transport, and general handling for use in therapeutic applications.

SUMMARY

[0009a] In a first aspect of the present disclosure, there is provided a composition comprising solid crystalline, impact- or detonation-insensitive particles comprising the compound of Formula I:



(Formula I),

or a pharmaceutically acceptable salt thereof.

[0009b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the composition as disclosed herein, and a pharmaceutically acceptable carrier.

[0009c] In yet another aspect of the present disclosure, there is provided a mixture comprising the composition as disclosed herein or the pharmaceutical composition as disclosed herein, and a blood sample.

[0009d] In a further aspect of the present disclosure, there is provided a method of producing a crystalline form of the compound of Formula I, the method comprising the steps of:

(a) dissolving the compound of Formula I in tetrahydrofuran;

(b) adding the solution of step (a) to n-heptane with stirring; and

(c) cooling the solution produced by step (b), thereby to provide the crystalline form of Formula I.

[0009e] In another aspect of the present disclosure, there is provided a crystalline form of the compound of Formula I produced by the method as disclosed herein.

[0009f] In yet another aspect of the present disclosure, there is provided a use of the composition as disclosed herein, the pharmaceutical composition as disclosed herein, or the mixture as disclosed herein, in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0009g] In a further aspect of the present disclosure, there is provided a use of a composition as disclosed herein or a pharmaceutical composition as disclosed herein or a mixture as disclosed herein, in the manufacture of a medicament for treating or preventing an ischemic or hypoxic condition in a subject in need thereof.

[0009h] In another aspect of the present disclosure, there is provided a use of a composition as disclosed herein, the pharmaceutical composition as disclosed herein, or the mixture as disclosed herein, in the manufacture of a medicament for protecting against normal tissue toxicity caused by chemotherapy and/or radiation therapy, wherein the composition, pharmaceutical composition or the mixture is to be subcutaneously administered to the subject in need thereof before the subject is to be exposed to the chemotherapy and/or radiation therapy.

[0009i] In yet another aspect of the present disclosure, there is provided a use of a composition as disclosed herein, the pharmaceutical composition as disclosed herein, or the mixture as disclosed herein, in the manufacture of a medicament for treating a disorder selected from the group consisting of an autoimmune disorder, inflammatory disorder, neurodegenerative disorder, and neuromuscular disorder in a subject in need thereof, wherein the composition, pharmaceutical composition, or the mixture is to be administered to the patient and is effective to ameliorate a symptom of the disorder, and thereafter a maintenance dose of the composition as disclosed herein, the pharmaceutical composition as disclosed herein, or the mixture as disclosed herein is to be further administered to maintain the amelioration of the symptom for a prolonged period of time.

[0009j] In a further aspect of the present disclosure, there is provided a use of a composition as disclosed herein, the pharmaceutical composition as disclosed herein, or the mixture as disclosed herein, in the manufacture of a medicament for increasing compliance and tolerability in a subject in need of treatment for an autoimmune disorder, inflammatory disorder, neurodegenerative disorder, or neuromuscular disorder, wherein the composition, pharmaceutical composition or the mixture does not cause hematologic, neurologic, pulmonary, metabolic,

cardiovascular, dermatologic, nephrologic, gastrointestinal, genitourinary, inflammatory, autoimmune, thyroidal, and immunodeficiency-related side effects; and wherein the subject completes treatment with a cumulative dose of at least 1 mg or 1 mg/m^2 of RRx-001 or an analog thereof.

[0009k] In another aspect of the present disclosure, there is provided a use of a composition as disclosed herein, the pharmaceutical composition as disclosed herein, or the mixture as disclosed herein, in the manufacture of a medicament for preventing the initiation, development or worsening of a symptom of a disorder selected from the group consisting of an autoimmune disorder, inflammatory disorder, neurodegenerative disorder, and neuromuscular disorder in a subject in need thereof.

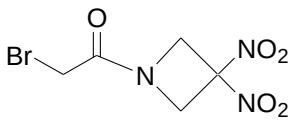
[0009l] In yet another aspect of the present disclosure, there is provided a use of a composition as disclosed herein, the pharmaceutical composition as disclosed herein, or the mixture as disclosed herein, in the manufacture of a medicament for enhancing physical performance of a mammal.

[0009m] In a further aspect of the present disclosure, there is provided a use of a composition as disclosed herein, the pharmaceutical composition as disclosed herein, or the mixture as disclosed herein, in the manufacture of a medicament for preventing or treating pulmonary hypertension (PH) in a patient.

[0009n] In yet another aspect of the present disclosure, there is provided a composition disclosed herein, the pharmaceutical composition disclosed herein, or the mixture disclosed herein, for use in therapy.

[0010] The present disclosure is based, in part, upon the discovery of a new impact- and shock- and detonation-insensitive form of ABDNAZ, its manufacture and use.

[0011] In one example, provided is a composition comprising solid crystalline, impact- or detonation-insensitive particles comprising the compound of Formula I:



(Formula I), or a pharmaceutically acceptable salt thereof. In some examples, the composition comprises the compound in a solvated form. In some

examples, the composition comprises tetrahydrofuran (THF). In some examples, the concentration of THF in the composition is at least about 330 ppm. In some examples, the particles are in a clathrated form. In some examples, the particles comprise THF. In some examples, the concentration of THF in the particles is at least about 330 ppm. In some examples, the composition further comprises n-heptane. In some examples, the concentration of n-heptane in the composition is at least about 800 ppm. In some examples, the particles comprise n-heptane. In some examples, the concentration of n-heptane in the particles is at least about 800 ppm.

[0012] In some examples, the composition has a bulk density in the range of from 0.1 g/cm^3 to 0.6 g/cm^3. In some examples, the bulk density is from 0.15 g/cm^3 to 0.5 g/cm^3, from 0.15 g/cm^3 to 0.4 g/cm^3, or from 0.16 g/cm^3 to 0.3 g/cm^3. In some examples, the particles have a bulk density less than about 0.45 g/cm^3. In some examples, Dv(10) of the particles is less than about 40 μm. In some examples, Dv(50) of the particles is less than about 200 μm. In some examples, Dv(90) of the particles is less than about 400 μm. In some examples,

the particles have a substantially needle-like shape. In some examples, the composition has a solubility greater than about 20 mg/mL in DMSO at 25°C. In some examples, the particles have an angle of repose of less than about 45 degrees.

[0013] In some examples, viability of cancer cells treated with the composition is lower than viability of cancer cells treated with an impact- or detonation-sensitive composition comprising equal amount of ABDNAZ. In some examples, viability of HCT 116 cells treated with about 8 μM ABDNAZ from the composition is at least about 50% lower than viability of HCT 116 cells treated with about 8 μM ABDNAZ from an impact- or detonation-sensitive composition. In some examples, viability of SCC VII cells treated with about 4 μM ABDNAZ from the composition is at least about 25% lower than viability of SCC VII cells treated with about 4 μM ABDNAZ from an impact- or detonation-sensitive composition. In some examples, viability of A549 cells treated with about 20 μM ABDNAZ from the composition is at least about 25% lower than viability of A549 cells treated with about 20 μM ABDNAZ from an impact- or detonation-sensitive composition. In some examples, the measurements are made about 24 hours after each treatment.

[0014] In some examples, viability of HCT 116 cells treated with about 10 μM ABDNAZ from the composition is less than about 25% of viability of untreated HCT 116 cells. In some examples, viability of SCC VII cells treated with about 4 μM ABDNAZ from the composition is less than about 50% of viability of untreated SCC VII cells. In some examples, viability of A549 cells treated with about 20 μM ABDNAZ from the composition is less than about 50% of viability of untreated A549 cells. In some examples, the measurements are made about 24 hours after each treatment.

[0015] In some examples, the particles are dispersed in a dedusting agent. In some examples, the dedusting agent is polyethylene glycol.

[0016] In some example, provided are pharmaceutical compositions comprising the composition described herein and a pharmaceutically acceptable carrier. In some examples, the pharmaceutical composition further comprises N,N-dimethylacetamide. In some examples, the pharmaceutical composition further comprises an anti-coagulant.

[0017] In some example, provided are mixtures comprising the composition described herein or the pharmaceutical composition described herein and a blood sample. In some examples,

the blood sample is an autologous blood sample or has been harvested from a subject to be treated with the compound. In some examples, the concentration of the compound of Formula I is from 0.1 mg/mL of blood to 10 mg/mL of blood.

[0018] In another example, the present disclosure provides a method of producing a crystalline form of the compound of Formula I, the method comprising the steps of: (a) dissolving the compound of Formula I in tetrahydrofuran, (b) adding the solution of step (a) to n-heptane with stirring, and (c) cooling the solution produced by step (b), to produce a crystalline form of Formula I. In some examples, the THF solution produced in step (a) is combined with the n-heptane in step (b) at a ratio of between about 1:3 (v/v) and about 1:10 (v/v). In some examples, during step (b), the adding occurs over a period between about 10 minutes and about 6 hours.

[0019] In one example, provided are crystalline forms of the compound of Formula I having the features described herein.

[0020] In some examples, the composition described herein is impact insensitive as determined by using a Series 3 Type (a)(ii) Test as set forth in the United Nations Manual of Tests and Criteria, seventh edition, 2019 by exposing a 40 mm^3 sample of the composition to 40 J of energy. In some examples, the crystalline form described herein is impact insensitive as determined by using a Series 3 Type (a)(ii) Test as set forth in the United Nations Manual of Tests and Criteria, seventh edition, 2019 by exposing a 40 mm^3 sample of the crystalline form to 40 J of energy.

[0021] In one example, provided herein are methods of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of the composition, the pharmaceutical composition, or the mixture described herein, thereby to treat the cancer in the subject. In another example, the present disclosure provides a method of treating cancer or protecting non-malignant tissue from damage associated with radiation and/or chemotherapeutic treatment of cancers in a subject in need thereof, the method comprising administering to the subject an effective amount of the composition described herein, the pharmaceutical composition described herein, or the mixture described herein, thereby to treat the cancer in the subject. In some examples, the composition or the pharmaceutical composition described herein is combined with blood harvested from the subject to create a mixture, whereupon the mixture is administered to the subject.

[0022] In one example, provided herein are methods of treating or preventing an ischemic or hypoxic condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the composition described herein, a pharmaceutical composition described herein, or a mixture described herein, is also provided. In some examples, the ischemic condition is an acute or chronic ischemic condition. In some examples, the acute ischemic condition is myocardial infarction, ischemic stroke, pulmonary embolism, perinatal hypoxia, circulatory shock, mountain sickness or acute respiratory failure. In some examples, the chronic ischemic condition is atherosclerosis, chronic venous insufficiency, chronic heart failure, cardiac cirrhosis, diabetes, macular degeneration, sleep apnea, Raynaud's disease, systemic sclerosis, nonbacterial thrombotic endocarditis, occlusive artery disease, angina pectoris, transient ischemic attacks, or chronic alcoholic liver disease. In some examples, the hypoxic condition is cancer, gastric or duodenal ulcers, liver or renal disease, thrombocytopenia, a blood coagulation disorder, a chronic illness, a therapeutic intervention that produces anemia such as cancer chemotherapy or altitude sickness. In some examples, the cancer is bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma, lung squamous cell carcinoma, malignant melanoma, colorectal cancer, head and neck cancer, cervical cancer, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small-cell lung cancer (SCLC), triple negative breast cancer, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), EBV-positive DLBCL, primary mediastinal large B-cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma (HL), mantle cell lymphoma (MCL), multiple myeloma (MM), myeloid cell leukemia- 1 protein (Mcl-1), myelodysplasia syndrome (MDS), non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).

[0023] In some examples, the pharmaceutical composition in the method described herein comprises at least 0.5 mg of the compound of Formula I and is administered intravenously, nasally, otically, intraperitoneally, subcutaneously, or orally.

[0024] In one example, provided herein are methods of protecting against normal tissue toxicity caused by chemotherapy and/or radiation therapy, the method comprising: subcutaneously administering to a subject in need thereof an effective amount of the

composition, the pharmaceutical composition, or the mixture described herein before the subject is exposed to the chemotherapy and/or radiation therapy. In some examples, the subject has cancer. In some examples, the cancer is head and neck cancer. In some examples, at least about 0.5 mg of the compound of Formula I is administered to the subject. In some examples, from about 0.5 mg to 4 mg of the compound of Formula I is administered to the subject. In some examples, the amount of the compound of Formula I is administered in one or more divided injections. In some examples, the normal tissue toxicity is acute mucositis or dysphagia. In some examples, the mucositis is late mucositis.

[0025] In one example, provided herein are methods of treating a disorder selected from the group consisting of an autoimmune disorder, inflammatory disorder, neurodegenerative disorder, and neuromuscular disorder in a subject in need thereof, the method comprising administering a loading dose of the composition, the pharmaceutical composition, or the mixture described herein to the subject in an amount effective to ameliorate a symptom of the disorder, and thereafter administering a maintenance dose of the composition, the pharmaceutical composition, or the mixture described herein to maintain the amelioration of the symptom for a prolonged period of time.

[0026] In one example, provided herein are methods for increasing compliance and tolerability in a subject in need of treatment for an autoimmune disorder, inflammatory disorder, neurodegenerative disorder, or neuromuscular disorder, the method comprising administering a therapeutically effective amount of the composition, the pharmaceutical composition, or the mixture described herein; wherein administration of the therapeutically effective amount does not cause hematologic, neurologic, pulmonary, metabolic, cardiovascular, dermatologic, nephrologic, gastrointestinal, genitourinary, inflammatory, autoimmune, thyroidal, and immunodeficiency-related side effects; and wherein the subject completes treatment with a cumulative dose of at least 1 mg or 1 mg/m^2 of RRx-001 or an analog thereof.

[0027] In one example, provided herein are methods of preventing the initiation, development or worsening of a symptom of a disorder selected from the group consisting of an autoimmune disorder, inflammatory disorder, neurodegenerative disorder, and neuromuscular disorder in a subject in need thereof, the method comprising administering an effective amount of the

composition, the pharmaceutical composition, or the mixture described herein to the subject to prevent the initiation, development, or worsening of the symptom of the disorder.

[0028] In one example, provided herein are methods of preventing the initiation, development or worsening of a symptom of a disorder selected from the group consisting of an autoimmune disorder, inflammatory disorder, neurodegenerative disorder, and neuromuscular disorder in a subject in need thereof, the method comprising administering an effective amount of the composition, the pharmaceutical composition, or the mixture described herein to the subject to prevent the initiation, development, or worsening of the symptom of the disorder.

[0029] In one example, provided herein are methods for enhancing physical performance of a mammal, the method comprising: administering an effective amount of the composition, the pharmaceutical composition, or the mixture described herein to said mammal prior to said physical performance.

[0030] In one example, provided herein are methods for preventing or treating pulmonary hypertension (PH) in a patient, the method comprising: administering a therapeutically effective amount of the composition, the pharmaceutical composition, or the mixture described herein.

[0031] In another example, the present disclosure provides a crystalline form of the compound of Formula I produced by the methods described herein. In some examples, the composition can comprise the compound in a solvated form, where the solvent can be, for example, tetrahydrofuran (THF). Alternatively, or in addition, the composition can comprise the particles in a clathrated form, where the particles can comprise, for example, THF. In another example, the present disclosure provides a pharmaceutical composition comprising a composition as described herein.

DESCRIPTION OF THE FIGURES

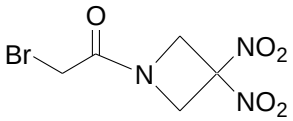
[0032] The present application can be understood by reference to the following description taken in conjunction with the accompanying figures.

[0033] **FIGS. 1A-1C** depict graphs plotting relative cell viability as a function of sample dose.

[0034] **FIG. 2** depicts a graph plotting turbidity as a function of sample concentration.

We claim:

1. A composition comprising solid crystalline, impact- or detonation-insensitive particles comprising the compound of Formula I:



(Formula I),

or a pharmaceutically acceptable salt thereof.

2. The composition of claim 1, wherein the composition comprises the compound in a solvated form.

3. The composition of claim 1 or 2, wherein the composition comprises tetrahydrofuran (THF).

4. The composition of claim 3, wherein the concentration of THF in the composition is at least about 330 ppm.

5. The composition of any one of claims 1-4, wherein the particles are in a clathrated form.

6. The composition of any one of claims 1-5, wherein the particles comprise THF.

7. The composition of claim 6, wherein the concentration of THF in the particles is at least about 330 ppm.

8. The composition of any one of claims 1-7, wherein the composition further comprises n-heptane.

9. The composition of claim 8, wherein the concentration of n-heptane in the composition is at least about 800 ppm.

10. The composition of any one of claims 1-9, wherein the particles comprise n-heptane.

11. The composition of claim 10, wherein the concentration of n-heptane in the particles is at least about 800 ppm.

12. The composition of any one of claims 1-11, wherein the composition has a bulk density in the range of from 0.1 g/cm^3 to 0.6 g/cm^3.

13. The composition of any one of claims 1-12, wherein the bulk density is from 0.15 g/cm^3 to 0.5 g/cm^3, from 0.15 g/cm^3 to 0.4 g/cm^3, or from 0.16 g/cm^3 to 0.3 g/cm^3.

14. The composition of any one of claims 1-13, wherein the particles have a bulk density less than about 0.45 g/cm^3.

15. The composition of any one of claims 1-14, wherein Dv(10) of the particles is less than about 40 µm.

16. The composition of any one of claims 1-15, wherein Dv(50) of the particles is less than about 200 µm.

17. The composition of any one of claims 1-16, wherein Dv(90) of the particles is less than about 400 µm.

18. The composition of any one of claims 1-17, wherein the particles have a substantially needle-like shape.

19. The composition of any one of claims 1-18, wherein the composition has a solubility greater than about 20 mg/mL in DMSO at 25°C.

20. The composition of any one of claims 1-19, wherein the particles have an angle of repose of less than about 45 degrees.

21. The composition of any one of claims 1-20, wherein viability of cancer cells treated with the composition is lower than viability of cancer cells treated with an impact- or detonation-sensitive composition comprising equal amount of ABDNAZ.

22. The composition of any one of claims 1-21, wherein (i) viability of HCT 116 cells treated with about 8 µM ABDNAZ from the composition is at least about 50% lower than viability of HCT 116 cells treated with about 8 µM ABDNAZ from an impact- or detonation-sensitive composition; (ii) viability of SCC VII cells treated with about 4 µM ABDNAZ from the composition is at least about 25% lower than viability of SCC VII cells treated with about 4 µM ABDNAZ from an impact- or detonation-sensitive composition; or (iii) viability of A549 cells treated with about 20 µM ABDNAZ from the composition is at least about 25% lower than viability of A549 cells treated with about 20 µM ABDNAZ from an impact- or detonation-sensitive composition; as measured 24 hours after each treatment.

23. The composition of any one of claims 1-21, wherein (i) viability of HCT 116 cells treated with about 10 μM ABDNAZ from the composition is less than about 25% of viability of untreated HCT 116 cells; (ii) viability of SCC VII cells treated with about 4 μM ABDNAZ from the composition is less than about 50% of viability of untreated SCC VII cells; or (iii) viability of A549 cells treated with about 20 μM ABDNAZ from the composition is less than about 50% of viability of untreated A549 cells; as measured 24 hours after each treatment.

24. The composition of any one of claims 1-23, wherein the particles are dispersed in a dedusting agent.

25. The composition of claim 24, wherein the dedusting agent is polyethylene glycol.

26. A pharmaceutical composition comprising the composition of any one of claims 1-25, and a pharmaceutically acceptable carrier.

27. The pharmaceutical composition of claim 26, further comprising N,N-dimethylacetamide.

28. The pharmaceutical composition of claim 26 or 27, further comprising an anti-coagulant.

29. A mixture comprising the composition of any one of claims 1-25 or the pharmaceutical composition of any one of claims 26-28, and a blood sample.

30. The mixture of claim 29, wherein the blood sample has been harvested from a subject to be treated with the compound.

31. The mixture of claim 30, wherein the concentration of the compound of Formula I is from 0.1 mg/mL of blood to 10 mg/mL of blood.

32. A method of producing a crystalline form of the compound of Formula I, the method comprising the steps of:

(a) dissolving the compound of Formula I in tetrahydrofuran;

(b) adding the solution of step (a) to n-heptane with stirring; and

(c) cooling the solution produced by step (b), thereby to provide the crystalline form of Formula I.

33. The method of claim 32, wherein the THF solution produced in step (a) is combined with the n-heptane in step (b) at a ratio of between about 1:3 (v/v) and about 1:10 (v/v).

34. The method claim 32 or 33, wherein, during step (b), the adding occurs over a period between about 10 minutes and about 6 hours.

35. A crystalline form of the compound of Formula I produced by the method of any one of claims 32-34.

36. The composition of any one of claims 1-25, wherein the composition is impact insensitive as determined by using a Series 3 Type (a)(ii) Test as set forth in the United Nations Manual of Tests and Criteria, seventh edition, 2019 by exposing a 40 mm^3 sample of the composition to 40 J of energy.

37. The crystalline form of the compound of claim 35, wherein the crystalline form is impact insensitive as determined by using a Series 3 Type (a)(ii) Test as set forth in the United Nations Manual of Tests and Criteria, seventh edition, 2019 by exposing a 40 mm^3 sample of the crystalline form to 40 J of energy.

38. Use of the composition of any one of claims 1-25, the pharmaceutical composition of any one of claims 26-28, or the mixture of any one of claims 29-31, in the manufacture of a medicament for treating cancer in a subject in need thereof.

39. The use of claim 38, wherein the composition of any one of claims 1-25 or the pharmaceutical composition of any one of claims 26-28 is combined with blood harvested from the subject to create a mixture, whereupon the mixture is to be administered to the subject.

40. Use of a composition of any one of claims 1-25 or a pharmaceutical composition of any one of claims 26-28 or a mixture of any one of claims 29-31, in the manufacture of a medicament for treating or preventing an ischemic or hypoxic condition in a subject in need thereof.

41. The use of claim 40, wherein the ischemic condition is an acute or chronic ischemic condition.

42. The use of claim 41, wherein the acute ischemic condition is myocardial infarction, ischemic stroke, pulmonary embolism, perinatal hypoxia, circulatory shock, mountain sickness or acute respiratory failure.

43. The use of claim 41, wherein the chronic ischemic condition is atherosclerosis, chronic venous insufficiency, chronic heart failure, cardiac cirrhosis, diabetes, macular degeneration, sleep apnea, Raynaud's disease, systemic sclerosis, nonbacterial thrombotic endocarditis, occlusive artery disease, angina pectoris, transient ischemic attacks, or chronic alcoholic liver disease.

44. The use of claim 40, wherein the hypoxic condition is cancer, gastric or duodenal ulcers, liver or renal disease, thrombocytopenia, a blood coagulation disorder, a chronic illness, a therapeutic intervention that produces anemia such as cancer chemotherapy or altitude sickness.

45. The use of claim 44, wherein the cancer is bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma, lung squamous cell carcinoma, malignant melanoma, colorectal cancer, head and neck cancer, cervical cancer, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small-cell lung cancer (SCLC), triple negative breast cancer, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), EBV-positive DLBCL, primary mediastinal large B-cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma (HL), mantle cell lymphoma (MCL), multiple myeloma (MM), myeloid cell leukemia- 1 protein (Mcl-1), myelodysplasia syndrome (MDS), non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).

46. The use of any one of claims 38-45, wherein the pharmaceutical composition comprises at least 0.5 mg of the compound of Formula I and is to be administered intravenously, nasally, otically, intraperitoneally, subcutaneously, or orally.

47. Use of a composition of any one of claims 1-25, the pharmaceutical composition of any one of claims 26-28, or the mixture of any one of claims 29-31, in the manufacture of a medicament for protecting against normal tissue toxicity caused by chemotherapy and/or radiation therapy, wherein the composition, pharmaceutical composition or the mixture is to be subcutaneously administered to the subject in need thereof before the subject is to be exposed to the chemotherapy and/or radiation therapy.

48. The use of claim 47, wherein the subject has cancer.

49. The use of claim 48, wherein the cancer is head and neck cancer.

50. The use of any one of claims 47-49, wherein at least about 0.5 mg of the compound of Formula I is to be administered to the subject.

51. The use of claim 50, wherein from about 0.5 mg to 4 mg of the compound of Formula I is to be administered to the subject.

52. The use of claim 50 or 51, wherein the amount of the compound of Formula I is to be administered in one or more divided injections.

53. The use of any one of claims 47-52, wherein the normal tissue toxicity is acute mucositis or dysphagia.

54. The use of claim 53, wherein the mucositis is late mucositis.

55. Use of a composition of any one of claims 1-25, the pharmaceutical composition of any one of claims 26-28, or the mixture of any one of claims 29-31, in the manufacture of a medicament for treating a disorder selected from the group consisting of an autoimmune disorder, inflammatory disorder, neurodegenerative disorder, and neuromuscular disorder in a subject in need thereof, wherein the composition, pharmaceutical composition, or the mixture is to be administered to the patient and is effective to ameliorate a symptom of the disorder, and thereafter a maintenance dose of the composition of any one of claims 1-25, the pharmaceutical composition of any one of claims 26-28, or the mixture of any one of claims 29-31 is to be further administered to maintain the amelioration of the symptom for a prolonged period of time.

56. Use of a composition of any one of claims 1-25, the pharmaceutical composition of any one of claims 26-28, or the mixture of any one of claims 29-31, in the manufacture of a medicament for increasing compliance and tolerability in a subject in need of treatment for an autoimmune disorder, inflammatory disorder, neurodegenerative disorder, or neuromuscular disorder, wherein the composition, pharmaceutical composition or the mixture does not cause hematologic, neurologic, pulmonary, metabolic, cardiovascular, dermatologic, nephrologic, gastrointestinal, genitourinary, inflammatory, autoimmune, thyroidal, and immunodeficiency-related side effects; and wherein the subject completes treatment with a cumulative dose of at least 1 mg or 1 mg/m^2 of RRx-001 or an analog thereof.

57. Use of a composition of any one of claims 1-25, the pharmaceutical composition of any one of claims 26-28, or the mixture of any one of claims 29-31, in the manufacture of a medicament for preventing the initiation, development or worsening of a symptom of a disorder selected from the group consisting of an autoimmune disorder, inflammatory disorder, neurodegenerative disorder, and neuromuscular disorder in a subject in need thereof.

58. Use of a composition of any one of claims 1-25, the pharmaceutical composition of any one of claims 26-28, or the mixture of any one of claims 29-31, in the manufacture of a medicament for enhancing physical performance of a mammal.

59. Use of a composition of any one of claims 1-25, the pharmaceutical composition of any one of claims 26-28, or the mixture of any one of claims 29-31, in the manufacture of a medicament for preventing or treating pulmonary hypertension (PH) in a patient.

60. A composition of any one of claims 1-25, the pharmaceutical composition of any one of claims 26-28, or the mixture of any one of claims 29-31, for use in therapy.