pathological conditions involve aberrant cell proliferation and/or regulation. Solid cancers and exudative macular degeneration depend upon the recruitment of a new blood supply for continued growth as well as metastasis.

SUMMARY OF THE INVENTION

[0009] Provided herein are new formulations of anti-CD105 antibodies, pre-filled syringes containing the formulations, and the use of such formulations for treating angiogenesis-related disorders. The present application provides formulations that may be used for intravenous or intraocular administration of, for example, treatment of cancers associated with CD105 and ophthalmologic conditions.

[0010] In one aspect, provided herein is a formulation comprising from about 1 mg/ml to about 150 mg/ml of an anti-CD105 antibody, or antigen-binding fragment thereof, up to about 100 mM buffering agent, up to about 1 M polyol, and a pH of about 4.0 to about 7.5.

[0010a] In one aspect, provided herein is a formulation that comprises from 1 mg/ml to 150 mg/ml of an anti-CD105 antibody, or antigen-binding fragment thereof, from 10 to 20 mM of a buffering agent, up to 240 mM of a polyol, and a pH of from 5.3 to 5.7; wherein the buffering agent comprises histidine, and wherein the polyol comprises trehalose or sorbitol.

[0010b] In one aspect, provided herein is a formulation that comprises from 1 mg/ml to 150 mg/ml of an anti-CD105 antibody, or antigen-binding fragment thereof, from 10 to 20 mM of a buffering agent, up to 240 mM of a polyol, and a pH of from 3.8 to 4.2; wherein the buffering agent comprises acetate, and wherein the polyol comprises trehalose or sorbitol.

[0011] In one aspect, the formulation is stable following preparation, which can be tested according to conventional means. With respect to stability of the formulation over time, at least 95% of the anti-CD105 antibody, or antigen-binding fragment thereof, may be present as a monomer following storage at about 2 to 8°C for at least about 12 months as measured by size exclusion chromatography (SEC). In some embodiments, the buffering agent of such formulations is histidine or phosphate buffered saline. With respect to the stability of the formulation over time, at least 90% of the anti-CD105 antibody, or antigen-binding fragment thereof, may be present as a monomer following storage at about 25° C for at least about 6 months as measured by size exclusion chromatography (SEC). In some embodiments, the buffering agent of such formulations is acetate.

[0012] Further, the anti-CD105 antibody, or antigen-binding fragment thereof, may display from about 50 to about 150% binding by a CD105 ELISA binding assay after storage at about 2 to 8°C for at least about 12 months.

[0013] The average isoelectric point (pI) of the anti-CD105 antibody may be from about 8.7 to about 9.2 after storage at 2 to 8°C for at least about 12 months, as measured by, for example, capillary electrophoresis-isoelectric focusing.

[0014] One would understand that the anti-CD105 antibody, or antigen-binding fragment thereof, may be stable for at least about 12 months, at least about 18 months, at least about 24 months, at least about 30 months, at least about 36 months, or more.

[0015] A formulation may contain at least 95% of the anti-CD105 antibody present as monomer as measured by SEC following freezing and thawing cycles of the formulation. Alternatively, or

from about 200 mM to about 300 mM trehalose or sucrose. In one embodiment, a formulation may comprise about 240 mM trehalose or sucrose.

[0029] Alternatively, the sugar may be sorbitol in an amount (concentration) of from about 200 mM to about 300 mM. In one embodiment, a formulation may comprise about 240 mM sorbitol.

[0030] Further non-limiting examples of a formulation provided herein is any one of formulations 1-39 of Table 1.

[0031] A formulation provided herein may have a pH of about 4.0 to about 7.5. In one embodiment, a formulation provided herein may have a pH of about 4.5, about 5.0, about 5.5, about 6.0, about 6.5, or about 7.0.

[0032] In one embodiment, formulations provided herein do not contain a surfactant. Optionally, in some cases, a surfactant can be included in the formulations. Non-limiting examples of surfactants include polysorbate 20, polysorbate 80 and Pluronic® F68.

[0033] Also provided herein is a pre-filled syringe suitable for intravenous or intravitreal administration comprising a formulation described herein. Such pre-filled syringes may be packaged and labeled for use for treatment of an angiogenesis-related condition such as any of the conditions described herein. Packages may further include directions for storage and administration. Provided herein is a package containing one or more pre-filled syringes suitable for intravenous or intravitreal administration comprising the formulation of any of the preceding claims.

[0034] One embodiment of the present application contemplates the use of any of the compositions described herein to formulate a medicament for treating a disorder described herein. Medicaments can be formulated based on the physical characteristics of the patient/subject needing treatment, and can be formulated in single or multiple formulations. Medicaments can be packaged in a suitable package with appropriate labels for the distribution to hospitals and clinics wherein the label is for the indication of treating a disorder as described herein in a subject. Medicaments can be packaged as a single or multiple units. Instructions for the dosage and administration of the compositions described herein can be included with the packages.

[0034a] In one aspect, provided herein is a use of a formulation as descrived herein, in the manufacture of a medicament for the treatment of an angiogenesis-related disease in a subject in need thereof.

[0035] Provided herein is a method of treating an angiogenesis-related disease in a patient (subject) in need thereof, comprising administering to said patient a formulation described herein. Such formulations may be administered to the patient intravitreally or intravenously.

[0036] An angiogenesis-related disease described herein may be, for example, a cancer or a metastasis. In one embodiment, the cancer is a solid tumor. Cancers to be treated include, for example, an epithelial based tumor. Non-limiting examples of cancers to be treated with such

CLAIMS

WHAT IS CLAIMED IS:

1. A formulation that comprises from 1 mg/ml to 150 mg/ml of an anti-CD105 antibody, or antigen-binding fragment thereof, from 10 to 20 mM of a buffering agent, up to 240 mM of a polyol, and a pH of from 5.3 to 5.7; wherein the buffering agent comprises histidine, and wherein the polyol comprises trehalose or sorbitol.

2. The formulation of claim 1, that comprises 240 mM trehalose.

3. The formulation of claim 1, that comprises 240 mM sorbitol.

4. The formulation of claim 1, that comprises 10 mM histidine.

5. The formulation of claim 1, that comprises 20 mM histidine.

6. The formulation of claim 1, that further comprises a surfactant.

7. The formulation of claim 6, wherein the surfactant comprises polysorbate 20, polysorbate 80 or PLURONIC® F68.

8. The formulation of claim 1, wherein the pH is 5.3, 5.4, 5.5, 5.6, or 5.7.

9. The formulation of claim 1, wherein the pH is from 5.4 to 5.6.

10. A pre-filled syringe suitable for intravenous administration comprising the formulation of any one of claims 1-9.

11. A pre-filled syringe suitable for intravitreal administration comprising a formulation of any one of claims 1-9.

12. Use of a formulation of any one of claims 1-8, in the manufacture of a medicament for the treatment of an angiogenesis-related disease in a subject in need thereof.

13. The use of claim 12, wherein the formulation is to be administered intravitreally.

14. The use of claim 12, wherein the formulation is to be administered intravenously.

15. The use of claim 12, wherein the angiogenesis-related disease comprises a cancer or a metastasis thereof.

16. The use of claim 15, wherein the cancer or the metastasis thereof comprises a solid tumor.

17. The use of claim 15, wherein the cancer or the metastasis thereof comprises a lung cancer, a melanoma, a breast cancer, a pancreatic cancer, an ovarian cancer, a colorectal cancer, a prostate cancer, a kidney cancer, a liver cancer, a uterine cancer, a neck cancer, a sarcoma, a myeloma, a brain cancer, or a lymphoma.

18. The use of claim 17, wherein the cancer or the metastasis thereof comprises the sarcoma and the sarcoma comprises an angiosarcoma.

19. The use of claim 12, wherein the angiogenesis-related disease comprises an ophthalmologic condition.

20. The use of claim 19, wherein the ophthalmologic condition comprises age-related macular degeneration, diabetic retinopathy, or choroidal neovascularization.

21. The use of claim 20, wherein the ophthalmologic condition comprises age-related macular degeneration, and the age related macular degeneration (AMD) comprises wet AMD or dry AMD.

22. The use of claim 12, wherein the formulation is to be administered to the subject one or more times.

23. The use of claim 12, wherein the formulation is to be administered to the subject once per day, once per week, once per month, once bi-monthly, once every two months, once every three months, once every four months, once every 5 months, or once every 6 months.

24. A formulation that comprises from 1 mg/ml to 150 mg/ml of an anti-CD105 antibody, or antigen-binding fragment thereof, from 10 to 20 mM of a buffering agent, up to 240 mM of a polyol, and a pH of from 3.8 to 4.2; wherein the buffering agent comprises acetate, and wherein the polyol comprises trehalose or sorbitol.

25. The formulation of claim 24, that comprises 240 mM trehalose.

26. The formulation of claim 24, that comprises 240 mM sorbitol.

27. The formulation of claim 24, that comprises 10 mM histidine.

28. The formulation of claim 24, that comprises 20 mM histidine.

29. The formulation of claim 24, that further comprises a surfactant.

30. The formulation of claim 29, wherein the surfactant comprises polysorbate 20, polysorbate 80 or PLURONIC® F68.

31. The formulation of claim 24, wherein the pH is 3.8, 3.9, 4.0, 4.1 or 4.2.

32. The formulation of claim 24, wherein the pH is from 3.9 to 4.1.

33. A pre-filled syringe suitable for intravenous administration comprising the formulation of any of claims 24-32.

34. A pre-filled syringe suitable for intravitreal administration comprising a formulation of any one of claims 24-32.

35. Use of a formulation of any one of claims 24-32, in the manufacture of a medicament for the treatment of an angiogenesis-related disease in a subject in need thereof.

36. The use of claim 35, wherein the formulation is to be administered intravitreally.

37. The use of claim 35, wherein the formulation is to be administered intravenously.

38. The use of claim 35, wherein the angiogenesis-related disease comprises a cancer or a metastasis thereof.

39. The use of claim 38, wherein the cancer or the metastasis thereof comprises a solid tumor.

40. The use of claim 38, wherein the cancer or the metastasis thereof comprises a lung cancer, a melanoma, a breast cancer, a pancreatic cancer, an ovarian cancer, a colorectal cancer, a prostate cancer, a kidney cancer, a liver cancer, a uterine cancer, a neck cancer, a sarcoma, a myeloma, a brain cancer, or a lymphoma.

41. The use of claim 40, wherein the cancer or the metastasis thereof comprises the sarcoma and the sarcoma comprises an angiosarcoma.

42. The use of claim 35, wherein the angiogenesis-related disease comprises an ophthalmologic condition.

43. The use of claim 42, wherein the ophthalmologic condition comprises age-related macular degeneration, diabetic retinopathy, or choroidal neovascularization.

44. The use of claim 43, wherein the ophthalmologic condition comprises age-related macular degeneration, and the age related macular degeneration (AMD) comprises wet AMD or dry AMD.

45. The use of claim 35, wherein the formulation is to be administered to the subject one or more times.

46. The use of claim 35, wherein the formulation is to be administered to the subject once per day, once per week, once per month, once bi-monthly, once every two months, once every three months, once every four months, once every 5 months, or once every 6 months.