[015] Clinical studies of two anti-TGF-beta antibodies showed mixed results in scleroderma trials. CAT-19, a recombinant human antibody that binds only TGF-beta1 with a dissociation constant of 150nM, shown no change in mRSS scores of the patients. A 2014 clinical study with fresolimumab, a high affinity human monoclonal antibody against all three TGF-beta isoforms, showed improvement in mRSS scores and downregulation of TGF-beta biomarkers in the skin. No further studies have been started or completed on anti-TGF-beta antibodies, and none are approved to treat scleroderma subjects.

[016] Clinical studies of rituximab, an anti-CD20 chimeric monoclonal antibody, have been completed. These studies have shown improvement in mRSS scores, but no improvement in lung function in a forced vital capacity test. There is some interest in the use of Rituximab as an alternative to cyclophosphamide for the treatment of scleroderma.

[017] Taking all these studies into account there is still a need for new therapies to treat scleroderma. Additional therapies to treat the symptoms of scleroderma would be useful, but a therapy which can reduce and repair the damage in scleroderma would be even more beneficial for patients, for example a drug that can reduce the fibrosis in scleroderma patients and cause the apoptosis of the cells responsible for the disease.

[018] Insulin-like growth factor proteins are essential in regulating cell growth and death. There are three types of proteins involved in the IGF system, including two insulin-like growth factor ligands (IGF1 and IGF2), two insulin-like growth factor receptors (IGF-1R and IGF-2R), and 6 insulin-like growth factor binding proteins (IGFBP1-6). There are indications that IGF system plays a role in many forms of cancer and many autoimmune diseases. In these diseases there is a higher level of IGF present in the tissue and/or blood of the patients. Studies have shown a higher levels of IGF in the skin and blood of scleroderma patients. It is believed the higher level of IGF plays a role in preventing the normal apoptosis process of the cells involved. Therefore, stopping the overstimulation IGF pathway is expected to be beneficial to scleroderma patients.

SUMMARY

[018a] In one aspect, the present disclosure refers to the use of insulin-like growth factor-1 receptor (IGF-1R) inhibitor in the manufacture of a medicament for the treatment of scleroderma wherein a said medicament is to be administered to a subject in need thereof.

[018b] In another aspect, the present disclosure refers to the use of insulin-like growth factor-1 receptor (IGF-1R) inhibitor in the manufacture of a medicament for the treatment of interstitial lung disease (ILD).

[018c] In yet another aspect, the present disclosure refers to the use of insulin-like growth factor-1 receptor (IGF-1R) inhibitor in the manufacture of a medicament for reducing fibrosis and/or collagen production and/or collagen accumulation in a subject with scleroderma or interstitial lung disease (ILD).

BRIEF DESCRIPTION OF THE DRAWINGS

[019] Figure 1 shows an overview of the study design disclosed herein.

DETAILED DESCRIPTION

[020] Provided herein are antibodies against insulin-like growth factor 1 receptor (IGF-1R) for the use in the treatment of scleroderma.

CLAIMS

What is claimed is:

1. ~~A method of treating scleroderma comprising administering to a subject in need thereof a therapeutically effective amount of an~~ Use of insulin-like growth factor-1 receptor (IGF-1R) inhibitor in the manufacture of a medicament for the treatment of scleroderma, wherein said medicament is to be administered to a subject in need thereof.

2. The ~~method~~ use of claim 1, wherein the scleroderma is localized scleroderma.

3. The use~~method~~ of claim 2, wherein the localized scleroderma is morphea scleroderma or linear scleroderma.

4. The use~~method~~ of claim 1, wherein the scleroderma is systemic scleroderma.

5. The use~~method~~ of claim 4, wherein the systemic scleroderma is selected from the group consisting of limited cutaneous systemic scleroderma, systemic sclerosis sine scleroderma, and diffuse cutaneous systemic sclerosis.

6. The use~~method~~ of claim 5, wherein the systemic scleroderma is diffuse cutaneous systemic sclerosis.

7. ~~A method of treating interstitial lung disease (ILD) comprising administering to a subject in need thereof a therapeutically effective amount of an~~ Use of insulin-like growth factor-1 receptor (IGF-~~-~~1R) inhibitor in the manufacture of a medicament for the treatment of interstitial lung disease (ILD).

8. The ~~method~~ use of claim 7, wherein the ILD is idiopathic pulmonary fibrosis.

9. ~~A method of reducing fibrosis and/or collagen production and/or accumulation in a subject with scleroderma or interstitial lung disease (ILD), comprising administering to said subject a therapeutically effective amount of an~~Use of insulin-like growth factor-1 receptor (IGF-~~-~~1R) inhibitor in the manufacture of a medicament for reducing fibrosis and/or collagen production and/or collagen accumulation in a subject with scleroderma or interstitial lung disease (ILD).

10. The ~~method~~ use of claim 9, wherein the subject has scleroderma.

11. The use~~method~~ of claim 10, wherein the scleroderma is systemic scleroderma.

12. The use~~method~~ of claim 11, wherein the systemic scleroderma is selected from the group consisting of limited cutaneous systemic scleroderma, systemic sclerosis sine scleroderma, and diffuse cutaneous systemic sclerosis.

13. The use~~method~~ of claim 12, wherein the systemic scleroderma is diffuse cutaneous systemic sclerosis.

14. The use~~method~~ of claim 9, wherein reducing fibrosis and collagen production and/or accumulation is measured by the skin elasticity.

15. The use ~~method~~ of claim 14, wherein reducing fibrosis and collagen production and/or accumulation is measured as a decrease in the subject's modified Rodnan total skin score (mRSS or mRTSS).

16. The use~~method~~ of any of claim 9, wherein reducing fibrosis and collagen production and/or accumulation is measured as an increase in the subject's American College of Rheumatology-Composite Response Index in Systemic Sclerosis (ACR-CRISS) score.

17. The use~~method~~ of claim 9, wherein the subject has ILD.

18. The use~~method~~ of claim 17, wherein the ILD is idiopathic pulmonary fibrosis.

19. The use~~method~~ of any of claims 9-13, 17, and 18, wherein reducing fibrosis and collagen production and/or accumulation is measured as an improvement in the subject's lung function.

20. The ~~method~~use of ~~any of claims~~claim 19, wherein reducing fibrosis and collagen production and/or accumulation is measured as an increase in the subject's walking distance under the 6-minute-walk test (6MWT).

21. The ~~method~~use of claim 19, wherein the forced vital capacity (FVC) is improved by ≥ 5%.

22. The ~~method~~use of claim 19, wherein the oxygen diffusing capacity (DLCO) is improved.

23. The ~~method~~use of any of claims 1-22, wherein ~~the administration~~ said medicament is to be administered ~~is~~ by intradermal injection, subcutaneous injection, intravenous injection (including intravenous infusion), or by inhalation.

24. The ~~method~~use of any of claims 1-23, wherein the IGF-1R inhibitor is an antibody or antigen binding fragment thereof.

25. The ~~method~~use of claim 24, wherein the antibody, or antigen binding fragment thereof, is to be administered at a dosage of about 1 mg/kg to about 5 mg/kg as a first dose.

26. The ~~method~~use of claim 24, wherein the antibody, or antigen binding fragment thereof, is to be administered at a dosage of about 5 mg/kg to about 10 mg/kg as a first dose.

27. The ~~method~~use of claim 26, wherein the antibody, or antigen binding fragment thereof, is to be administered at a dosage of about 5 mg/kg to about 20 mg/kg in subsequent doses.

28. The ~~method~~use of claim 27, wherein the antibody, or antigen binding fragment thereof, is to be administered at a dosage of about 10 mg/kg as a first dose; and about 20 mg/kg in subsequent doses.

29. The ~~method~~use of claim 28, wherein the subsequent doses are to be administered every three weeks for at least 21 weeks.

30. The ~~method~~use of claim 24, wherein the antibody, or an antigen binding fragment thereof, has a binding affinity (K_D) of 10^{-8} M or less for IGF-1R.

31. The ~~method~~use of claim 30, wherein the antibody, or an antigen binding fragment thereof, has a binding affinity (K_D) of 10^{-13} to 10^{-9} M for the IGF-1R.

32. The ~~method~~use of claim 24, wherein the antibody, or an antigen binding fragment thereof, has an IC_{50} value for the binding of IGF-I and IGF-II to IGF-IR of no more than about 2 nM.

33. The ~~method~~use of claim 32, wherein the antibody, or an antigen binding fragment thereof, comprises a heavy chain comprising CDR1, CDR2, and CDR3 and a light chain comprising CDR1, CDR2 and CDR3, wherein the heavy chain CDR1, CDR2, and CDR3 amino acid sequences and light chain CDR1, CDR2, and CDR3 amino acid sequences are at least 90% identical to (i) the amino acid sequences of SEQ ID NOs:

85-90, respectively; or (ii) the amino acid sequences of SEQ ID NOs: 85, 93, 87, 88, 94, and 90, respectively.

34. The ~~method~~use of claim 33, wherein the antibody, or an antigen binding fragment thereof, comprises: (i) heavy chain CDR1, CDR2, and CDR3 amino acid sequences and light chain CDR1, CDR2, and CDR3 amino acid sequences as set forth in SEQ ID NOs: 85-90, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 amino acid sequences and light chain CDR1, CDR2, and CDR3 amino acid sequences as set forth in SEQ ID NOs: 85, 93, 87, 88, 94, and 90, respectively.

35. The ~~method~~use of claim 33, wherein the antibody, or an antigen binding fragment thereof, comprises: (i) a heavy chain variable region having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 91 and a light chain variable region having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 92; or (ii) a heavy chain variable region having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 95 and a light chain variable region having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 96.

36. The ~~method~~use of claim 33, wherein the antibody, or an antigen binding fragment thereof, comprises: (i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 91 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 92; or (ii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 95 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 96.

37. The ~~method~~use of claim 24, wherein the antibody is teprotumumab.

38. The ~~method~~use of any of claims 24-37, wherein the antibody, or an antigen binding fragment thereof, is a human antibody, a monoclonal antibody, a human monoclonal antibody, a purified antibody, a diabody, a single-chain antibody, a multi-specific antibody, Fab, Fab', F(ab')2, Fv or scFv.

39. The ~~method~~use of any of claims 24-37, wherein the antibody, or an antigen binding fragment thereof, is to be administered in a pharmaceutical composition that additionally comprises a pharmaceutically acceptable diluent or excipient or carrier.

40. The ~~method~~use of claim 39, additionally comprising ~~administering, as part of the pharmaceutical composition or separately,~~ one or more other pharmaceutically active

compounds for the treatment of morphea or linear scleroderma. to be administered as part of the pharmaceutical composition or separately.

41. The methoduse of claim 39, wherein the additionally comprising administering, as part of the pharmaceutical composition or separately, a compound chosen from: a corticosteroid; rituximab or another anti-CD20 antibody; tocilizumab or another anti-IL-6 antibody; or methotrexate to be administered as part of the pharmaceutical composition or separately.

42. The methoduse of any of claims 1-41, wherein the treatment is efficacious for at least 4 weeks beyond the last administered dose.

43. The methoduse of any of claims 1-41, wherein the treatment is efficacious for at least 6 weeks beyond the last administered dose.

44. The methoduse of any of claims 1-41, wherein the treatment is efficacious for at least 8 weeks beyond the last administered dose.

45. The methoduse of any of claims 1-41, wherein the treatment is efficacious for at least 20 weeks beyond the last administered dose.

46. The methoduse of any of claims 1-32 and 38-45 wherein said IGF-1R inhibitor is chosen from ganitumab, figitumumab, MEDI-573, cixutumumab, dalotuzumab, robatumumab, AVE1642, BIIB022, xentuzumab, istiratumab, linsitinib, picropodophyllin, BMS-754807, BMS-536924, BMS-554417, GSK1838705A, GSK1904529A, NVP-AEW541, NVP-ADW742, GTx-134, AG1024, KW-2450, PL-2258, NVP-AEW541, NSM-18, AZD3463, AZD9362, BI885578, BI893923, TT-100, XL-228, and A-928605.

47. The methoduse of claim 46 wherein said IGF-1R inhibitor is an antibody, or an antigen binding fragment thereof.

48. The methoduse of claim 47 wherein said IGF-1R inhibitor is a human, chimeric human, or humanized monoclonal antibody, or antigen binding fragment thereof, suitable for human therapy.

49. The methoduse of claim 47 wherein the antibody is to be administered intravenously (IV) or subcutaneously (SC).

50. The methoduse of claim 48 wherein the antibody is to be administered IV.

51. The ~~method~~use of claim 47 wherein said antibody is chosen from ganitumab, figitumumab, MEDI-573, cixutumumab, dalotuzumab, robatumumab, AVE1642, BIIB022, xentuzumab, and istiratumab.

52. The ~~method~~use of claim 51 wherein the antibody is ganitumab.

53. The ~~method~~use of claim 52 wherein the ganitumab is to be dosed at:

    a. 1-60 mg/kg or 75-4500 mg IV every 3 weeks; or

    b. 0.6-40 mg/kg or 45-3000 mg IV every 2 weeks; or

    c. 0.3-20 mg/kg; or 22-1500 mg IV weekly.

54. The ~~method~~use of claim 51 wherein the antibody is figitumumab.

55. The ~~method~~use of claim 54 wherein the figitumumab is to be dosed at:

    a. 1-60 mg/kg or 75-4500 mg IV every 3 weeks; or

    b. 0.6-40 mg/kg or 45-3000 mg IV every 2 weeks; or

    c. 0.3-20 mg/kg or 22-1500 mg IV weekly.

56. The ~~method~~use of claim 51 wherein the antibody is cixutumumab.

57. The ~~method~~use of claim 56 wherein the cixutumumab is to be dosed at:

    a. 1-45 mg/kg or 75-3400 mg IV every 3 weeks; or

    b. 0.6-30 mg/kg or 45-2300 mg IV every 2 weeks; or

    c. 0.3-15 mg/kg Or 22-1200 mg IV weekly.

58. The ~~method~~use of claim 51 wherein the antibody is dalotuzumab.

59. The ~~method~~use of claim 58 wherein the dalotuzumab is to be dosed at:

    a. 1-90 mg/kg or 75-6800 mg IV every 3 weeks; or

    b. 0.6-60 mg/kg or 45-4500 mg IV every 2 weeks; or

    c. 0.3-30 mg/kg or 22-2300 mg IV weekly.

60. The ~~method~~use of claim 51 wherein the antibody is robatumumab.

61. The ~~method~~use of claim 60 wherein the robatumumab is to be dosed at:

a. 1-75 mg/kg or 75-5700 mg IV every 3 weeks; or

b. 0.6-50 mg/kg or 45-3800 mg IV every 2 weeks; or

c. 0.3-25 mg/kg or 22-1900 mg IV weekly.

62. The ~~method~~use of claim 51 wherein the antibody is xentuzumab.

63. The ~~method~~use of claim 62 wherein the xentuzumab is to be dosed at:

a. 1-112 mg/kg or 75-8400 mg IV every 3 weeks; or

b. 0.6-75 mg/kg or 45-5700 mg IV every 2 weeks; or

c. 0.3-38 mg/kg or 22-2900 mg IV weekly.

64. The ~~method~~use of claim 51 wherein the antibody is istiratumab.

65. The ~~method~~use of claim 64 wherein the istiratumab is to be dosed at:

a. 1-112 mg/kg or 75-8400 mg IV every 3 weeks; or

b. 0.6-75 mg/kg or 45-5700 mg IV every 2 weeks; or

c. 0.3-38 mg/kg or 22-2900 mg IV weekly.

66. The ~~method~~use of claim 51 wherein the antibody is AVE1642.

67. The ~~method~~use of claim 66 wherein the AVE1642 is to be dosed at:

a. 1-60 mg/kg or 75-4500 mg IV every 3 weeks; or

b. 0.6-40 mg/kg or 45-3000 mg IV every 2 weeks; or

c. 0.3-20 mg/kg or 22-1500 mg IV weekly.

68. The ~~method~~use of claim 51 wherein the antibody is BIIB022.

69. The ~~method~~use of claim 68 wherein the BIIB022 is to be dosed at:

a. 1-75 mg/kg or 75-5700 mg IV every 3 weeks; or

b. 0.6-50 mg/kg; or 45-3800 mg IV every 2 weeks; or

c. 0.3-25 mg/kg or 22-1900 mg IV weekly.

70. The ~~method~~use of claim 47 wherein said IGF-1R inhibitor antibody comprises at least one heavy chain and at least one light chain selected from the selected from the group consisting of:

a. a heavy chain comprising the amino acid sequence of SEQ ID NO:7 and a light chain comprising the amino acid sequence SEQ ID NO:8;
b. a heavy chain comprising the amino acid sequence of SEQ ID NO:15 and a light chain comprising the amino acid sequence SEQ ID NO:16;
c. a heavy chain comprising the amino acid sequence of SEQ ID NO:23 and a light chain comprising the amino acid sequence SEQ ID NO:24;
d. a heavy chain comprising the amino acid sequence of SEQ ID NO:31 and a light chain comprising the amino acid sequence SEQ ID NO:32;
e. a heavy chain comprising the amino acid sequence of SEQ ID NO:39 and a light chain comprising the amino acid sequence SEQ ID NO:40;
f. a heavy chain comprising the amino acid sequence of SEQ ID NO:47 and a light chain comprising the amino acid sequence SEQ ID NO:48;
g. a heavy chain comprising the amino acid sequence of SEQ ID NO:55 and a light chain comprising the amino acid sequence SEQ ID NO:;
h. a heavy chain comprising the amino acid sequence of SEQ ID NO:63 and a light chain comprising the amino acid sequence SEQ ID NO:64;
i. a heavy chain comprising the amino acid sequence of SEQ ID NO:65 and a light chain comprising the amino acid sequence SEQ ID NO:66; and
j. a heavy chain comprising the amino acid sequence of SEQ ID NO:73 and a light chain comprising the amino acid sequence SEQ ID NO:74.
k. a heavy chain comprising the amino acid sequence of SEQ ID NO:31 and a light chain comprising the amino acid sequence SEQ ID NO:81;
l. a heavy chain comprising the amino acid sequence of SEQ ID NO:31 and a light chain comprising the amino acid sequence SEQ ID NO:82;
m. a heavy chain comprising the amino acid sequence of SEQ ID NO:31 and a light chain comprising the amino acid sequence SEQ ID NO:83;
n. a heavy chain comprising the amino acid sequence of SEQ ID NO:31 and a light chain comprising the amino acid sequence SEQ ID NO:84;
o. a heavy chain comprising the amino acid sequence of SEQ ID NO:79 and a light chain comprising the amino acid sequence SEQ ID NO:32;

p. a heavy chain comprising the amino acid sequence of SEQ ID NO:79 and a light chain comprising the amino acid sequence SEQ ID NO:81;

q. a heavy chain comprising the amino acid sequence of SEQ ID NO:79 and a light chain comprising the amino acid sequence SEQ ID NO:82;

r. a heavy chain comprising the amino acid sequence of SEQ ID NO:79 and a light chain comprising the amino acid sequence SEQ ID NO:83;

s. a heavy chain comprising the amino acid sequence of SEQ ID NO:79 and a light chain comprising the amino acid sequence SEQ ID NO:84.

71. The ~~method~~use of claim 46 wherein said IGF-1R inhibitor is a small molecule.

72. The ~~method~~use of claim 71 wherein said IGF-1R inhibitor is to be dosed orally.

73. The ~~method~~use of claim 71 wherein said IGF-1R inhibitor is chosen from linsitinib, picropodophyllin, BMS-754807, BMS-536924, BMS-554417, GSK1838705A, GSK1904529A, NVP-AEW541, NVP-ADW742, GTx-134, AG1024, KW-2450, PL-2258, NVP-AEW541, NSM-18, AZD3463, AZD9362, BI885578, BI893923, TT-100, XL-228, and A-928605.

74. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is linsitinib.

75. The ~~method~~use of claim 74 wherein the linsitinib is to be dosed at:

a. 10-750 mg orally once daily continuous dosing or 10-1500 mg/day for once daily intermittent dosing (for up to 7 days of every 14 days); or

b. 6-500 mg orally twice daily continuous dosing or 6-1000 mg for twice daily intermittent dosing (for up to 7 days of every 14 days); or

c. 3-250 mg orally three-times daily continuous dosing or 3-500 mg for three-times daily intermittent dosing (for up to 7 days of every 14 days).

76. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is picropodophyllin.

77. The ~~method~~use of claim 76 wherein the picropodophyllin is to be dosed:

a. orally once daily at 20-2000 mg; or

b. orally twice daily at 13-1400 mg

c. orally three times daily at 6-700 mg.

78. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is BMS-754807.

79. The ~~method~~use of claim 78 wherein the BMS-754807 is to be dosed:

    a. once daily at 5-600 mg orally; or

    b. twice daily at 3-400 mg orally; or

    c. three times daily at 1-200 mg.

80. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is BMS-536924.

81. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is BMS-554417.

82. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is GSK1838705A.

83. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is GSK1904529A.

84. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is NVP-AEW541.

85. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is NVP-ADW742.

86. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is GTx-134.

87. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is AG1024.

88. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is PL-2258.

89. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is NVP-AEW541.

90. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is NSM-18.

91. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is AZD3463.

92. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is AZD9362.

93. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is BI885578.

94. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is BI893923.

95. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is TT-100.

96. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is XL-228.

97. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is A-928605.

98. The ~~method~~use of any of claims 80-97 wherein the IGF-1R inhibitor is to be dosed:

a. once daily at 1-2000 mg orally; or

b. twice daily at 0.6-1400 mg orally; or

c. three times daily at 0.3-700 mg orally.

99. The ~~method~~use of claim 73 wherein the IGF-1R inhibitor is KW-2450.

100. The ~~method~~use of claim 99 wherein the KW-2450 is to be dosed:

a. once daily at 1-100 mg orally; or

b. twice daily at 0.6-70 mg orally; or

c. three times daily at 0.3-30 mg orally.

101. The ~~method~~use of any of claims 24-39 and 47-70, wherein the anti-insulin-like growth factor-1 receptor (IGF-1R) antibody or an antigen binding fragment thereof comprises a modification in the Fc region to extend the half-life.