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 insulin-like growth factor-1 receptor (IGF-1R) inhibitor.

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

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

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

5. The 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 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 insulin-like growth factor-1 receptor (IGF 1R) inhibitor.

8. The method 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 insulin-like growth factor-1 receptor (IGF 1R) inhibitor .

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

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

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

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

15. The 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 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 method of claim 9, wherein the subject has ILD.

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

19. The 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 of any of claims 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 of claim 19, wherein the forced vital capacity (FVC) is improved by $\geq 5\%$.

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

23. The method of any of claims 1-22, wherein the administration is by intradermal injection, subcutaneous injection, intravenous injection (including intravenous infusion), or by inhalation.

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

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

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

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

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

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

30. The method 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 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 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 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 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 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 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 of claim 24, wherein the antibody is teprotumumab.

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

40. The method 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.

41. The method 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.

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

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

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

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

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

48. The method 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 method of claim 47 wherein the antibody is administered intravenously (IV) or subcutaneously (SC).

50. The method of claim 48 wherein the antibody is administered IV.

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

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

53. The method of claim 52 wherein the ganitumab is 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 of claim 51 wherein the antibody is figitumumab.

55. The method of claim 54 wherein the figitumumab is 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 of claim 51 wherein the antibody is cixutumumab.

57. The method of claim 56 wherein the cixutumumab is 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 of claim 51 wherein the antibody is dalotuzumab.

59. The method of claim 58 wherein the dalotuzumab is 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 of claim 51 wherein the antibody is robatumumab.

61. The method of claim 60 wherein the robatumumab is 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 of claim 51 wherein the antibody is xentuzumab.

63. The method of claim 62 wherein the xentuzumab is 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 of claim 51 wherein the antibody is istiratumab.

65. The method of claim 64 wherein the istiratumab is 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 of claim 51 wherein the antibody is AVE1642.

67. The method of claim 66 wherein the AVE1642 is 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 of claim 51 wherein the antibody is BIIB022.

69. The method of claim 68 wherein the BIIB022 is 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 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 of claim 46 wherein said IGF-1R inhibitor is a small molecule.

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

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

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

77. The method of claim 76 wherein the picropodophyllin is 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 of claim 73 wherein the IGF-1R inhibitor is BMS-754807.

79. The method of claim 78 wherein the BMS-754807 is 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 of claim 73 wherein the IGF-1R inhibitor is BMS-536924.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

98. The method of any of claims 80-97 wherein the IGF-1R inhibitor is 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 of claim 73 wherein the IGF-1R inhibitor is KW-2450.

100. The method of claim 99 wherein the KW-2450 is 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 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.