Claims

It is claimed:

1. An isolated GHR antagonist antibody that specifically binds to human and cynomolgus monkey growth hormone receptor (GHR) and, when administered to a subject, lowers a level of insulin-like growth factor-1 (IGF-1) in blood of said subject.

2. The isolated GHR antagonist antibody of claim 1, wherein the antibody comprises an antigen binding region that competes with monoclonal antibody SS1 for binding to human GHR.

3. The isolated GHR antagonist antibody of claim 1, wherein the antibody recognizes an epitope that is the same as or overlaps with the epitope on human GHR recognized by monoclonal antibody SS1.

4. The isolated GHR antagonist antibody of any one of claims 1 to 3, wherein the antibody binds to human GHR with an equilibrium dissociation constant of less than about 10 nM.

5. The isolated GHR antagonist antibody of any one of claims 1 to 4, wherein the antibody comprises a heavy chain variable region and a light chain variable region.

6. An isolated GHR antagonist antibody that specifically binds to growth hormone receptor (GHR) and comprises: a heavy chain variable region (VH) complementary determining region one (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, 15 or 16, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 114 or 115, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 118, a light chain variable region (VL) CDR1 comprising the amino acid sequence of SEQ ID NO: 99, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 106.

7. An isolated GHR antagonist antibody that specifically binds to growth hormone receptor (GHR) and comprises: a heavy chain variable region (VH) comprising a VH complementary determining region one (CDR1), VH CDR2, and VH CDR3 of the VH sequence of SEQ ID NO: 8; and a light chain variable region (VL) comprising a VL CDR1, VL CDR2, and VL CDR3.

8. The isolated GHR antagonist antibody of claim 7, wherein the VL comprises a CDR1, VL CDR2, and VL CDR3 of the VL sequence of SEQ ID NO: 7.

9. The isolated GHR antagonist antibody of any of claims 6 to 8, wherein the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 1, 15 or 16, the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 2 or 17, the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 3, the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 4, the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 5, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 6.

10. The isolated GHR antagonist antibody of claim 9, wherein the VH comprises the amino acid sequence of SEQ ID NO: 8 or a variant thereof with one or several conservative amino acid substitutions in residues that are not within a CDR, and the VL comprises the amino acid sequence of SEQ ID NO: 7 or a variant thereof with one or several amino acid substitutions in amino acids that are not within a CDR.

11. The isolated GHR antagonist antibody of any one of claims 6 to 10, wherein the antibody further comprises an immunologically inert constant region.

12. The isolated GHR antagonist antibody of claim 11, wherein the antibody has an isotype that is selected from the group consisting of IgG_2, $IgG_{2\Delta a}$, IgG_4, $IgG_{4\Delta b}$, $IgG_{4\Delta c}$, IgG_4 S228P, $IgG_{4\Delta b}$ S228P and $IgG_{4\Delta c}$ S228P.

13. The isolated GHR antagonist antibody of claim 11, wherein the constant region is aglycosylated Fc.

14. The isolated GHR antagonist antibody of claim 10, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 134 or 133, and a light chain comprising the amino acid sequence of SEQ ID NO: 135.

15. A pharmaceutical composition comprising the antibody of any one of claims 1 to 14.

16. A cell line that recombinantly produces the antibody of any one of claims 1 to 14.

17. A nucleic acid encoding a heavy chain variable region and/or a light chain variable region of the antibody of any one of claims 1 to 14.

18. A method for reducing a level of insulin-like growth factor-1 (IGF-1) in blood of an individual in need thereof, comprising administering to the individual a therapeutically effective amount of the antibody of any one of claims 1 to 14.

19. The method of claim 18, wherein the level of IGF-1 is reduced at least about 40%.

20. The method of claim 18, wherein the level of IGF-1 is reduced at least about 60%.

21. The method of claim 18, wherein the individual has a diseased selected from the group consisting of acromegaly, gigantism, cancer, diabetic nephropathy, arthritis, and lung inflammation.

22. A method for treating acromegaly in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of the antibody of any one of claims 1 to 14.

23. A method for treating gigantism in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of the antibody of any one of claims 1 to 14.

24. A method for treating cancer in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of the antibody of any one of claims 1 to 14.

25. A method for treating diabetic nephropathy in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of the antibody of any one of claims 1 to 14.

26. A method for treating lung inflammation in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of the antibody of any one of claims 1 to 14.

27. A method for treating arthritis in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of the antibody of any one of claims 1 to 14.

Claims

It is claimed:

1. An isolated GHR antagonist antibody that specifically binds to human and cynomolgus monkey growth hormone receptor (GHR) and, when administered to a subject, lowers a level of insulin-like growth factor-1 (IGF-1) in blood of said subject.

2. The isolated GHR antagonist antibody of claim 1, wherein the antibody comprises an antigen binding region that competes with monoclonal antibody SS1 for binding to human GHR.

3. The isolated GHR antagonist antibody of claim 1, wherein the antibody recognizes an epitope that is the same as or overlaps with the epitope on human GHR recognized by monoclonal antibody SS1.

4. The isolated GHR antagonist antibody of any one of claims 1 to 3, wherein the antibody binds to human GHR with an equilibrium dissociation constant of less than about 10 nM.

5. The isolated GHR antagonist antibody of any one of claims 1 to 4, wherein the antibody comprises a heavy chain variable region and a light chain variable region.

6. An isolated GHR antagonist antibody that specifically binds to growth hormone receptor (GHR) and comprises: a heavy chain variable region (VH) complementary determining region one (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, 15 or 16, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 114 or 115, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 118, a light chain variable region (VL) CDR1 comprising the amino acid sequence of SEQ ID NO: 99, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 106.

7. An isolated GHR antagonist antibody that specifically binds to growth hormone receptor (GHR) and comprises: a heavy chain variable region (VH) comprising a VH complementary determining region one (CDR1), VH CDR2, and VH

CDR3 of the VH sequence of SEQ ID NO: 8; and a light chain variable region (VL) comprising a VL CDR1, VL CDR2, and VL CDR3.

8. The isolated GHR antagonist antibody of claim 7, wherein the VL comprises a CDR1, VL CDR2, and VL CDR3 of the VL sequence of SEQ ID NO: 7.

9. The isolated GHR antagonist antibody of any of claims 6 to 8, wherein the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 1, 15 or 16, the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 2 or 17, the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 3, the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 4, the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 5, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 6.

10. The isolated GHR antagonist antibody of claim 9, wherein the VH comprises the amino acid sequence of SEQ ID NO: 8 or a variant thereof with one or several conservative amino acid substitutions in residues that are not within a CDR, and the VL comprises the amino acid sequence of SEQ ID NO: 7 or a variant thereof with one or several amino acid substitutions in amino acids that are not within a CDR.

11. The isolated GHR antagonist antibody of any one of claims 6 to 10, wherein the antibody further comprises an immunologically inert constant region.

12. The isolated GHR antagonist antibody of claim 11, wherein the antibody has an isotype that is selected from the group consisting of IgG_2, $IgG_{2\Delta a}$, IgG_4, $IgG_{4\Delta b}$, $IgG_{4\Delta c}$, IgG_4 S228P, $IgG_{4\Delta b}$ S228P and $IgG_{4\Delta c}$ S228P.

13. The isolated GHR antagonist antibody of claim 11, wherein the constant region is aglycosylated Fc.

14. The isolated GHR antagonist antibody of claim 10, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 134 or 133, and a light chain comprising the amino acid sequence of SEQ ID NO: 135.

15. A pharmaceutical composition comprising the antibody of any one of claims 1 to 14.

16. A cell line that recombinantly produces the antibody of any one of claims 1 to 14.

17. A nucleic acid encoding a heavy chain variable region and/or a light chain variable region of the antibody of any one of claims 1 to 14.

18. The antibody of any one of claims 1 to 14 for use in reducing a level of insulin-like growth factor-1 (IGF-1) in blood of an individual in need thereof.

19. Use of the antibody of any one of claims 1 to 14 in the manufacture of a medicament for reducing a level of insulin-like growth factor-1 (IGF-1) in blood of an individual in need thereof.

20. The antibody of claim 18, wherein the level of IGF-1 is reduced at least about 40%.

21. The use of claim 19, wherein the level of IGF-1 is reduced at least about 40%.

22. The antibody of claim 18, wherein the level of IGF-1 is reduced at least about 60%.

23. The use of claim 19, wherein the level of IGF-1 is reduced at least about 60%.

24. The antibody of claim 18, wherein the individual has a disease selected from the group consisting of acromegaly, gigantism, cancer, diabetic nephropathy, arthritis, and lung inflammation.

25. The use of claim 19, wherein the individual has a disease selected from the group consisting of acromegaly, gigantism, cancer, diabetic nephropathy, arthritis, and lung inflammation.

26. The antibody of any one of claims 1 to 14 for use in the treatment of acromegaly in an individual in need thereof.

27. Use of the antibody of any one of claims 1 to 14 in the manufacture of a medicament for the treatment of acromegaly in an individual in need thereof.

28. The antibody of any one of claims 1 to 14 for use in the treatment of gigantism in an individual in need thereof.

29. Use of the antibody of any one of claims 1 to 14 in the manufacture of a medicament for the treatment of gigantism in an individual in need thereof.

30. The antibody of any one of claims 1 to 14 for use in the treatment of cancer in an individual in need thereof.

31. Use of the antibody of any one of claims 1 to 14 in the manufacture of a medicament for the treatment of cancer in an individual in need thereof.

32. The antibody of any one of claims 1 to 14 for use in the treatment of diabetic nephropathy in an individual in need thereof.

33. Use of the antibody of any one of claims 1 to 14 in the manufacture of a medicament for the treatment of diabetic nephropathy in an individual in need thereof.

34. The antibody of any one of claims 1 to 14 for use in the treatment of lung inflammation in an individual in need thereof.

35. Use of the antibody of any one of claims 1 to 14 in the manufacture of a medicament for the treatment of lung inflammation in an individual in need thereof.

36. The antibody of any one of claims 1 to 14 for use in the treatment of arthritis in an individual in need thereof.

37. Use of the antibody of any one of claims 1 to 14 in the manufacture of a medicament for the treatment of arthritis in an individual in need thereof.