WHAT IS CLAIMED IS:

1. A fully human isolated specific binding protein that preferentially binds to insulin-like growth factor-II (IGF-II) with cross-reactivity to insulin-like growth factor I (IGF-I) and neutralizes IGF-I and IGF-II activity.

2. The specific binding protein of Claim 1, wherein said binding protein binds to IGF-II with at least 2.5 times greater affinity than to IGF-I.

3. The specific binding protein of Claim 1, wherein said binding protein has an EC_{50} of no more than 15 nM for inhibiting IGF-I-dependent IGF-I receptor phosphorylation in NIH3T3 cells expressing IGF-1R ectopically.

4. The specific binding protein of Claim 1, wherein said binding protein has an EC_{50} of no more than 5 nM for inhibiting IGF-II-dependent IGF-I receptor phosphorylation in NIH3T3 cells expressing IGF-1R ectopically.

5. The specific binding protein of Claim 1, wherein said binding protein inhibits greater than 70% of IGF-II dependent proliferation of NIH3T3 cells that express recombinant hIGF-IR with an EC_{50} of no more than 25 nM.

6. The specific binding protein of Claim 1, wherein said binding protein inhibits greater than 70% of IGF-I dependent proliferation of NIH3T3 cells that express recombinant hIGF-IR with an EC_{50} of no more than 40 nM.

7. The specific binding protein of Claim 1, wherein said binding protein competes for binding with monoclonal antibody comprising a variable heavy chain sequence selected from the group consisting of SEQ ID NO.: 2, SEQ ID NO.: 6, SEQ ID NO.: 10, SEQ ID NO.: 14 and SEQ ID NO.: 18.

8. The specific binding protein of Claim 7, wherein said monoclonal antibody comprises a variable light chain sequence selected from the group consisting of SEQ ID NO.: 4, SEQ ID NO.: 8, SEQ ID NO.: 12 and SEQ ID NO.: 16.

9. The specific binding protein of any of Claims 1-8, wherein said binding protein binds to IGF-I with a K_D of less than 4 nM.

10. The specific binding protein of any of Claims 1-8, wherein said binding protein binds to IGF-I with a K_D of less than 650 pM.

11. The specific binding protein of any of Claims 1-8, wherein said binding protein binds to IGF-II with a K_D of less than 300 pM.

12. The specific binding protein of any of Claims 1-8, wherein said binding protein is a fully human monoclonal antibody.

13. The specific binding protein of any of Claims 1-8, wherein said binding protein is a binding fragment of a fully human monoclonal antibody.

14. The specific binding protein of Claim 13, wherein said binding fragment is selected from the group consisting of Fab, Fab' or $F(ab')_2$ and Fv.

15. The specific binding protein of any of Claims 1-8, wherein said binding protein is monoclonal antibody 7.251.3 (ATCC Accession Number PTA-7422).

16. The specific binding protein of any of Claims 1-8, wherein said binding protein is monoclonal antibody 7.34.1 (ATCC Accession Number PTA-7423).

17. The specific binding protein of any of Claims 1-8, wherein said binding protein is monoclonal antibody 7.159.2 (ATCC Accession Number PTA-7424).

18. The specific binding protein of any of Claims 1-8, wherein said binding protein comprises a heavy chain polypeptide having the sequence of SEQ ID NO.: 6.

19. The specific binding protein of any of Claims 1-8, wherein said binding protein comprises a light chain polypeptide having the sequence of SEQ ID NO.: 8.

20. The specific binding protein of any of Claims 1-8, wherein said binding protein comprises a heavy chain polypeptide having the sequence of SEQ ID NO.: 10.

21. The specific binding protein of any of Claims 1-8, wherein said binding protein comprises a light chain polypeptide having the sequence of SEQ ID NO.: 12.

22. The specific binding protein of any of Claims 1-8, wherein said binding protein comprises a heavy chain polypeptide having the sequence of SEQ ID NO.: 14.

23. The specific binding protein of any of Claims 1-8, wherein said binding protein comprises a light chain polypeptide having the sequence of SEQ ID NO.: 16.

24. The specific binding protein of any of Claims 1-8 in a mixture with a pharmaceutically acceptable carrier.

25. A nucleic acid molecule encoding the specific binding protein of Claim 1.

26. A vector comprising the nucleic acid molecule of Claim 25.

27. A host cell comprising the vector of Claim 26.

28. The human monoclonal antibody of Claim 12, wherein said antibody does not bind specifically to IGF-II or IGF-I proteins when said proteins are bound to Insulin Growth Factor Binding Proteins.

29. A method of determining the level of insulin-like growth factor-II (IGF-II) and insulin-like growth factor I (IGF-I) in a patient sample comprising:

providing a patient sample;

contacting said sample with the binding protein of Claim 1; and

determining the level of IGF-I and IGF-II in said sample.

30. The method according to Claim 29 wherein the patient sample is blood.

31. Use of the specific binding protein of any one of Claims 1-8 in the preparation of a medicament for the treatment of a malignant tumor.

32. The use of Claim 31, where said binding protein is a fully human monoclonal antibody.

33. The use of Claim 31, wherein said malignant tumor is selected from the group consisting of: melanoma, non-small cell lung cancer, glioma, hepatocellular (liver) carcinoma, thyroid tumor, gastric (stomach) cancer, prostrate cancer, breast cancer, ovarian cancer, bladder cancer, lung cancer, glioblastoma, endometrial cancer, kidney cancer, colon cancer, pancreatic cancer, and epidermoid carcinoma.

34. The use of Claim 32, wherein the binding protein is mAb 7.251.3 (ATCC Accession Number PTA-7422) or mAb 7.34.1 (ATCC Accession Number PTA-7423) or mAb 7.159.2 (ATCC Accession Number PTA-7424).

35. The use of Claim 31, wherein said medicament is for use in combination with a second anti-neoplastic agent selected from the group consisting of an antibody, a chemotherapeutic agent, and a radioactive drug.

36. The use of Claim 31, wherein said medicament is for use in conjunction with or following a conventional surgery, a bone marrow stem cell transplantation or a peripheral stem cell transplantation.

37. Use of the specific binding protein of any one of Claims 1-8 in the preparation of a medicament for the treatment of a growth factor-dependent disease.

38. The use of Claim 37, wherein said binding protein is a fully human monoclonal antibody.

39. The use of Claim 38, wherein the antibody is selected from the group consisting of mAb 7.251.3 (ATCC Accession Number PTA-7422), mAb 7.34.1 (ATCC Accession Number PTA-7423), and mAb 7.159.2 (ATCC Accession Number PTA-7424).

40. The use of Claim 37, wherein the growth factor-dependent disease is selected from the group consisting of: osteoporosis, diabetes, and cardiovascular diseases.

41. A method of treating a malignant tumor in a mammal, comprising:

selecting a mammal in need of treatment for a malignant tumor; and

administering to said mammal a therapeutically effective dose of the specific binding protein of Claim 1.

42. The method of Claim 41, wherein said animal is human.

43. The method of Claim 41, where said binding protein is a fully human monoclonal antibody.

44. The method of Claim 41, wherein said malignant tumor is selected from the group consisting of: melanoma, non-small cell lung cancer, glioma, hepatocellular (liver) carcinoma, thyroid tumor, gastric (stomach) cancer, prostrate cancer, breast cancer, ovarian cancer, bladder cancer, lung cancer, glioblastoma, endometrial cancer, kidney cancer, colon cancer, pancreatic cancer, and epidermoid carcinoma.

45. The method of Claim 41, wherein the binding protein is selected from the group consisting of mAb 7.251.3 (ATCC Accession Number PTA-7422), mAb 7.34.1 (ATCC Accession Number PTA-7423), and mAb 7.159.2 (ATCC Accession Number PTA-7424).

46. A method of treating a growth factor-dependent disease in a mammal, comprising:

selecting a mammal in need of treatment for a growth factor-dependent disease; and

administering to said mammal a therapeutically effective dose of the specific binding protein of Claim 1.

47. The method of Claim 46, wherein said mammal is human.

48. The method of Claim 46, wherein said binding protein is a fully human monoclonal antibody.

49. The method of Claim 46, wherein the antibody is selected from the group consisting of mAb 7.251.3 (ATCC Accession Number PTA-7422), mAb 7.34.1 (ATCC Accession Number PTA-7423), and mAb 7.159.2 (ATCC Accession Number PTA-7424).

50. The method of Claim 46, wherein the growth factor-dependent disease is selected from the group consisting of: osteoporosis, diabetes, and cardiovascular diseases.

51. A conjugate comprising the antibody of Claim 12 or a binding fragment thereof and a therapeutic agent.

52. The conjugate of Claim 51, wherein the therapeutic agent is a toxin.

53. The conjugate of Claim 51, wherein the therapeutic agent is a radioisotope.

54. The conjugate of Claim 51, wherein the therapeutic agent is a pharmaceutical composition.

55. The specific binding protein of any of Claims 1-8, wherein said binding protein, or binding fragment thereof, comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of "Ser Tyr Tyr Trp Ser" (SEQ ID NO: 21);

a heavy chain complementarity determining region 2 (CDR2) having the amino acid sequence of "Tyr Phe Phe Tyr Ser Gly Tyr Thr Asn Tyr Asn Pro Ser Leu Lys Ser" (SEQ ID NO: 22);

a heavy chain complementarity determining region 3 (CDR3) having the amino acid sequence of "Ile Thr Gly Thr Thr Lys Gly Gly Met Asp Val" (SEQ ID NO: 23);

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of "Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Asp Val His" (SEQ ID NO: 24);

a light chain complementarity determining region 2 (CDR2) having the amino acid sequence of "Gly Asn Asn Asn Arg Pro Ser" (SEQ ID NO: 25); and

a light chain complementarity determining region 3 (CDR3) having the amino acid sequence of "Gln Ser Phe Asp Ser Ser Leu Ser Gly Ser Val" (SEQ ID NO: 26).

56. The specific binding protein of any of Claims 1-8, wherein said binding protein, or binding fragment thereof, comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of "Ser Tyr Tyr Trp Ser" (SEQ ID NO: 27);

a heavy chain complementarity determining region 2 (CDR2) having the amino acid sequence of "Tyr Phe Phe Tyr Ser Gly Tyr Thr Asn Tyr Asn Pro Ser Leu Lys Ser" (SEQ ID NO: 28);

a heavy chain complementarity determining region 3 (CDR3) having the amino acid sequence of "Ile Thr Gly Thr Thr Lys Gly Gly Met Asp Val" (SEQ ID NO: 29);

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of "Thr Gly Arg Ser Ser Asn Ile Gly Ala Gly Tyr Asp Val His" (SEQ ID NO: 30);

a light chain complementarity determining region 2 (CDR2) having the amino acid sequence of "Gly Asn Ser Asn Arg Pro Ser" (SEQ ID NO: 31); and

a light chain complementarity determining region 3 (CDR3) having the amino acid sequence of "Gln Ser Tyr Asp Ser Ser Leu Ser Gly Ser Val" (SEQ ID NO: 32).

57. The specific binding protein of any of Claims 1-8, wherein said binding protein, or binding fragment thereof, comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of "Ser Tyr Asp Ile Asn" (SEQ ID NO: 33);

a heavy chain complementarity determining region 2 (CDR2) having the amino acid sequence of "Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln Gly" (SEQ ID NO: 34);

a heavy chain complementarity determining region 3 (CDR3) having the amino acid sequence of "Asp Pro Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val" (SEQ ID NO: 35);

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of "Ser Gly Ser Ser Ser Asn Ile Glu Asn Asn His Val Ser" (SEQ ID NO: 36);

a light chain complementarity determining region 2 (CDR2) having the amino acid sequence of "Asp Asn Asn Lys Arg Pro Ser" (SEQ ID NO: 37); and

a light chain complementarity determining region 3 (CDR3) having the amino acid sequence of "Glu Thr Trp Asp Thr Ser Leu Ser Ala Gly Arg Val" (SEQ ID NO: 38).

Claims

1. A fully human isolated specific binding protein that preferentially binds to insulin-like growth factor-II (IGF-II) with cross-reactivity to insulin-like growth factor I (IGF-I) and neutralizes IGF-I and IGF-II activity, wherein said binding protein, or binding fragment thereof, comprises:

   a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of "Ser Tyr Asp Ile Asn" (SEQ ID NO: 33);
   a heavy chain complementarity determining region 2 (CDR2) having the amino acid sequence of "Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln Gly" (SEQ ID NO: 34);
   a heavy chain complementarity determining region 3 (CDR3) having the amino acid sequence of "Asp Pro Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val" (SEQ ID NO: 35);
   a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of "Ser Gly Ser Ser Ser Asn Ile Glu Asn Asn His Val Ser" (SEQ ID NO: 36);
   a light chain complementarity determining region 2 (CDR2) having the amino acid sequence of "Asp Asn Asn Lys Arg Pro Ser" (SEQ ID NO: 37); and
   a light chain complementarity determining region 3 (CDR3) having the amino acid sequence of "Glu Thr Trp Asp Thr Ser Leu Ser Ala Gly Arg Val" (SEQ ID NO: 38).

2. The specific binding protein of claim 1, wherein said binding protein is monoclonal antibody 7.159.2 (ATCC Accession Number PTA-7424).

3. The specific binding protein of claim 1, wherein said binding protein comprises a heavy chain polypeptide having the sequence of SEQ ID NO.: 6;
   or wherein said binding protein comprises a light chain polypeptide having the sequence of SEQ ID NO.: 8.

4. The specific binding protein of any of Claims 1 or 3, wherein said binding protein comprises a heavy chain polypeptide having the sequence of SEQ ID NO.: 6; and wherein said binding protein comprises a light chain polypeptide having the sequence of SEQ ID NO.: 8.

5. The specific binding protein of any one of the preceding claims, wherein said binding protein is a fully human monoclonal antibody; or a binding fragment of a fully human monoclonal antibody.

6. The specific binding protein of Claim 5, wherein said binding fragment is selected from the group consisting of Fab, Fab' or $F(ab')_2$ and Fv.

7. The specific binding protein of any of Claims 1 to 6 in a mixture with a pharmaceutically acceptable carrier.

8. A nucleic acid molecule encoding the specific binding protein of any one of claims 1 to 6.

9. A vector comprising the nucleic acid molecule of Claim 8.

10. A host cell comprising the vector of Claim 9.

11. The specific binding protein of any one of Claims 1 to 6, wherein said specific binding protein does not bind specifically to IGF-II or IGF-I proteins when said proteins are bound to Insulin Growth Factor Binding Proteins.

12. A method of determining the level of insulin-like growth factor-II (IGF-II) and insulin-like growth factor I (IGF-I) in a patient sample comprising:

contacting a sample from a patient with the specific binding protein of any one of claims 1 to 6; and
determining the level of IGF-I and IGF-II in said sample.

13. Use of the specific binding protein of any one of Claims 1 to 6 in the preparation of a medicament for the treatment of a malignant tumor.

14. The use of Claim 13, wherein said malignant tumor is selected from the group consisting of: melanoma, non-small cell lung cancer, glioma, hepatocellular (liver) carcinoma, thyroid tumor, gastric (stomach) cancer, prostrate cancer, breast cancer, ovarian cancer, bladder cancer, lung cancer, glioblastoma, endometrial cancer, kidney cancer, colon cancer, pancreatic cancer, and epidermoid carcinoma.

15. The use of Claim 13 or 14, wherein said medicament is for use in combination with a second anti-neoplastic agent selected from the group consisting of an antibody, a chemotherapeutic agent, and a radioactive drug.

16. The use of Claim 13 or 14, wherein said medicament is for use in conjunction with or following a conventional surgery, a bone marrow stem cell transplantation or a peripheral stem cell transplantation.

17. A conjugate comprising the antibody of Claim 5 or a binding fragment thereof and a therapeutic agent.

18. The conjugate of Claim 17, wherein the therapeutic agent is a toxin; a radioisotope; or a pharmaceutical composition.