WO 03/093317, JP 2003-310275, WO 2005/018671, WO 2005/028515, and WO 2005/027970.

For the treatment of human disease an antibody with a fully human sequence is highly desirable in order to minimize the risk of generating a human anti-antibody reaction and neutralizing antibodies that will rapidly eliminate the administered antibody from the body and thereby reduce the therapeutic effect. As such, and given the roles of IGF-1 and IGF-2 dependent signaling in the development and progression of cancers, it has become desirable to obtain fully human antibodies. WO 2007/070432 describes fully human antibodies that co-neutralise the mitogenic effects of both ligands.

It was an object of the ~~invention~~embodiments disclosed herein to provide alternative human anti-IGF antibodies with high affinities.

It was a further object of the ~~invention~~embodiments disclosed herein to provide human anti-IGF antibodies with high affinity to IGF-1.

It was a further object of the ~~invention~~embodiments disclosed herein to provide human anti-IGF antibodies with high affinity to IGF-1 and to IGF-2.

It was a further object of the ~~invention~~embodiments disclosed herein to provide human anti-IGF antibodies with adequate relative affinities to IGF-1 and to IGF-2.

It was a further object of the ~~invention~~embodiments disclosed herein to provide human anti-IGF antibodies with a higher affinity to IGF-1 than to IGF-2.

It was a further object of the ~~invention~~embodiments disclosed herein to provide human anti-IGF antibodies with high IGF-1 neutralisation potency.

It was a further object of the ~~invention~~embodiments disclosed herein to provide human anti-IGF antibodies with high IGF-1 and IGF-2 neutralisation potency.

It was a further object of the ~~invention~~embodiments disclosed herein to provide human anti-IGF antibodies with high solubility and stability.

It was a further object of the ~~invention~~embodiments disclosed herein to obtain antibodies that do not affect binding of insulin to its receptor.

The clinical development of therapeutic agents is supported by pharmacodynamic biomarkers of drug activity. Clinical studies with antibodies targeting the IGF-1R have demonstrated that an increase in total serum IGF-1 levels may be a useful pharmacodynamic marker for these agents (Pollack et al., 2007). The reason for the increase in total serum IGF-1 levels is likely due to a feedback mechanism involving pituitary growth hormone (GH) secretion which releases both IGF-1 and IGFBPs from the liver. Indeed, in humans it has been demonstrated that free or bioactive IGF-1, which represents only around 1 % of total IGF-1 levels, determines the feedback response (Chen et al., 2005).

It was therefore a further object of the ~~invention~~embodiments disclosed herein to provide, for the treatment of diseases in whose development and/or progression the IGFs are causally involved, a therapy that is accompanied by a biomarker that allows the pharmacological monitoring of the effectiveness of the therapy.

In a first aspect, there is provided an isolated human antibody molecule, which

a) binds to human IGF-1 and IGF-2 such that

i) binding of IGF-1 and IGF-2 to the IGF-1 receptor is prevented and

ii) IGF-1 receptor-mediated signaling is inhibited,

b) binds to mouse and rat IGF-1 and IGF-2,

c) does not bind to human insulin;

wherein said antibody molecule is

an antibody molecule that has heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:21 (CDR1), SEQ ID NO:22 (CDR2) and SEQ ID NO:23 (CDR3) and that has light chain CDRs comprising the amino acid sequences of SEQ ID NO:24 (CDR1), SEQ ID NO:25 (CDR2) and SEQ ID NO:26 (CDR3).

In a second aspect, there is provided a DNA molecule encoding the variable heavy chain and the variable light chain of an antibody molecule as defined herein.

In a third aspect, there is provided an expression vector containing a DNA molecule comprising the nucleotide sequence encoding the variable heavy chain and the variable light chain of an antibody molecule as defined herein.

In a fourth aspect, there is provided a host cell carrying one or more expression vectors as defined herein.

In a fifth aspect, there is provided a method for producing an antibody as defined herein, comprising transfecting a mammalian host cell with one or more vectors as defined herein, cultivating the host cell and recovering and purifying the antibody.

In a sixth aspect, there is provided a method for producing an antibody as defined herein, comprising obtaining a mammalian host cell comprising one or more vectors as defined herein, and cultivating the host cell.

In a seventh aspect, there is provided an antibody molecule as defined herein for use in medicine.

In an eighth aspect, there is provided an antibody molecule as defined herein for use in the treatment of a cancerous disease selected from cancers of the hematopoietic system including leukemias, lymphomas and myelomas, cancers of the gastrointestinal tract including esophageal, gastric, colorectal, pancreatic, liver and gall bladder cancer and bile duct cancer, in particular hepatocellular carcinoma; kidney, prostate and bladder cancer; gynecological cancers including breast, ovarian, cervical and endometrial cancer; skin and head and neck cancers including malignant melanomas; pediatric cancers like Wilms' tumour, neuroblastoma and Ewing's sarcoma; brain cancers like glioblastoma; sarcomas like osteosarcoma, soft tissue sarcoma, rhabdomyosarcoma, hemangiosarcoma; lung cancer, in particular non-small cell lung cancer; mesothelioma and thyroid cancer.

In a ninth aspect, there is provided a pharmaceutical composition comprising an antibody molecule as defined herein and a pharmaceutically acceptable carrier.

In a tenth aspect, there is provided an *in vitro* method for inhibiting the binding of IGF-1 and IGF-2 to the IGF-1 receptor in a mammalian cell, comprising administering to said cell an antibody molecule as defined herein, whereby signaling mediated by the IGF-1 receptor and proliferation and anti-apoptosis mediated by IGF-1 and IGF-2 are inhibited.

In an eleventh aspect, there is provided an *in vitro* method for inhibiting the binding of IGF-2 to the insulin receptor IR-A in a mammalian cell, comprising administering to said cell an antibody molecule as defined herein, whereby signaling mediated by the insulin receptor IR-A is inhibited and whereby proliferation and anti-apoptosis mediated by IGF-2 is inhibited.

In a twelfth aspect, there is provided an *in vitro* method for monitoring the effectiveness of a treatment of a cancer patient with an antibody molecule that binds to IGF-1 and IGF-2, wherein said antibody molecule as defined herein, wherein said method comprises

(a) measuring, in a biological sample of said patient, the level of total IGF-1,

(b) measuring, in a biological sample of said patient, the level of total IGF-1, after administering to said patient said anti IGF antibody molecule wherein the amount of increase in the level of total IGF-1, compared with the level of total IGF-1 measured in step (a), indicates to which extent the patient responds to the treatment with said anti-IGF antibody molecule.

In the experiments of the present ~~invention~~disclosure, it could be demonstrated that total serum IGF-1 levels are elevated upon application of the anti-IGF antibodies of the invention. Thus, total IGF-1 levels are a useful pharmacodynamic marker for the effectiveness of the therapy with an anti-IGF antibody. It is therefore highly advantageous that the antibodies of the invention are cross-reactive with IGFs from a suitable animal species, e.g. mouse or rat, such that a pharmacodynamic effect can already be tested pre-clinically.

Claims

1) An isolated human antibody molecule, which

a) binds to human IGF-1 and IGF-2 such that

i) binding of IGF-1 and IGF-2 to the IGF-1 receptor is prevented and

ii) IGF-1 receptor-mediated signaling is inhibited,

b) binds to mouse and rat IGF-1 and IGF-2,

c) does not bind to human insulin;

wherein said antibody molecule is ~~selected from the group comprising~~

~~i) an antibody molecule that has heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:1 (CDR1), SEQ ID NO:2 (CDR2) and SEQ ID NO:3 (CDR3) and that has light chain CDRs comprising the amino acid sequences of SEQ ID NO:4 (CDR1), SEQ ID NO:5 (CDR2) and SEQ ID NO:6 (CDR3);~~

~~ii) an antibody molecule that has heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:11 (CDR1), SEQ ID NO:12 (CDR2) and SEQ ID NO:13 (CDR3) and that has light chain CDRs comprising the amino acid sequences of SEQ ID NO:14 (CDR1), SEQ ID NO:15 (CDR2) and SEQ ID NO:16 (CDR3);~~

~~iii)~~ an antibody molecule that has heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:21 (CDR1), SEQ ID NO:22 (CDR2) and SEQ ID NO:23 (CDR3) and that has light chain CDRs comprising the amino acid sequences of SEQ ID NO:24 (CDR1), SEQ ID NO:25 (CDR2) and SEQ ID NO:26 (CDR3).

~~2) An anti-IGF antibody molecule, wherein said antibody molecule has heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:1 (CDR1), SEQ ID NO:2 (CDR2) and SEQ ID NO:3 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO:4 (CDR1), SEQ ID NO:5 (CDR2) and SEQ ID NO:6 (CDR3).~~

~~3) An anti-IGF antibody molecule, wherein said antibody molecule has heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:11 (CDR1), SEQ ID NO:12 (CDR2) and SEQ ID NO:13 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO:14 (CDR1), SEQ ID NO:15 (CDR2) and SEQ ID NO:16 (CDR3).~~

~~4) An anti-IGF antibody molecule, wherein said antibody molecule has heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:21 (CDR1), SEQ ID NO:22 (CDR2) and SEQ ID NO:23 (CDR3) and has light chain CDRs comprising the amino acid sequences of SEQ ID NO:24 (CDR1), SEQ ID NO:25 (CDR2) and SEQ ID NO:26 (CDR3).~~

~~5) The antibody molecule of claim 1 i) or 2, which has a variable heavy chain comprising the amino acid sequence of SEQ ID NO:8.~~

~~6) The antibody molecule of claim 1 i), 2, or 5, which has a variable light chain comprising the amino acid sequence of SEQ ID NO:10.~~

~~7) The antibody molecule of claim 1 ii) or 3, which has a variable heavy chain comprising the amino acid sequence of SEQ ID NO:18.~~

~~8) The antibody molecule of claim 1 ii), 3, or 7, which has a variable light chain comprising the amino acid sequence of SEQ ID NO:20.~~

~~9)~~ 2) The antibody molecule of claim 1 ~~iii) or 4~~, which has a variable heavy chain comprising the amino acid sequence of SEQ ID NO:28.

~~10)~~ 3) The antibody molecule of claim 1 ~~iii), 4 or 9~~, which has a variable light chain comprising the amino acid sequence of SEQ ID NO:30.

~~11)~~4) The antibody molecule of any one of claims 1 to ~~10~~3, comprising a heavy chain constant region selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgM, IgA and IgE constant regions.

~~12)~~5) The antibody molecule of claim ~~11~~4, wherein said heavy chain constant region is IgG1 comprising the amino acid sequence of SEQ ID NO:32.

~~13)~~6) The antibody molecule of any one of claims 1 to ~~10~~3, wherein the light chain constant region is Igλ.

~~14)~~7) The antibody molecule of claim ~~13~~6, wherein the light chain constant region comprises the amino acid sequence of SEQ ID NO:34.

~~15) The antibody molecule of claims 5 or 6 which has~~

~~a) a heavy chain comprising the amino acid sequence of SEQ ID NO:35, and~~

~~b) a light chain comprising the amino acid of SEQ ID NO:36.~~

~~16) The antibody molecule of claims 7 or 8 which has~~

~~a) a heavy chain comprising the amino acid sequence of SEQ ID NO:37, and~~

~~b) a light chain comprising the amino acid sequence of SEQ ID NO:38.~~

~~17)~~8) The antibody molecule of claims ~~9~~ 2 or ~~10~~ 3 which has

a) a heavy chain comprising the amino acid sequence of SEQ ID NO:39, and

b) a light chain comprising the amino acid sequence of SEQ ID NO:40.

~~18)~~ 9) The antibody molecule of any one of claims 1 to ~~10~~3, which is a Fab, $F(ab')_2$, or single chain Fv fragment .

~~19)~~ 10) A DNA molecule encoding the variable heavy chain ~~or~~ and the variable light chain of an antibody molecule of any one of claims 1 to ~~18~~9~~, or a fragment or variant thereof~~.

~~20)~~ 11) The DNA molecule of claim ~~19~~ 10 which has the nucleotide sequence of SEQ ID NO:~~7, 17 or~~ 27~~, respectively~~, encoding the variable heavy chain of the antibody defined in claim ~~5, 7 or 9~~2, ~~respectively~~ and which has the nucleotide sequence of SEQ ID NO: 29, encoding the variable light chain of the antibody defined in claim 3.

~~21) The DNA molecule of claim 19 which has the nucleotide sequence of SEQ ID NO:9, 19 or 29, respectively, encoding the variable light chain of the antibody defined in claim 6, 8 or 10, respectively.~~

~~22)~~ 12) An expression vector containing a DNA molecule comprising the nucleotide sequence encoding the variable heavy chain and~~/or~~ the variable light chain of an antibody molecule of any one of claims 1 to ~~18~~9.

~~23)~~ 13) The expression vector of claim ~~22~~ 12 containing a DNA molecule ~~comprising the nucleotide sequence of SEQ ID NO:7 and/or SEQ ID NO:9, or comprising the sequence of SEQ ID NO:17 and/or SEQ ID NO:19, or~~ comprising the sequence of SEQ ID NO:27 and/or SEQ ID NO:29.

~~24)~~ 14) The expression vector of claim ~~22~~ 12 or ~~23~~13, comprising, in addition, a DNA molecule encoding the constant heavy chain and/or the constant light chain, respectively, linked to the DNA molecule encoding the variable heavy chain and/or the variable light chain, respectively.

~~25)~~ 15) A host cell carrying one or more expression vectors of claim ~~22~~12, ~~23~~13, or ~~24~~14.

~~26)~~ 16) The host cell of claim ~~25~~15, which is a mammalian cell.

~~27)~~ 17) A method for producing an antibody of any one of claims 1 to ~~18~~9, comprising transfecting a mammalian host cell with one or more vectors of claim ~~22~~ 12 to ~~24~~14, cultivating the host cell and recovering and purifying the antibody.

~~28)~~18) A method for producing an antibody of any one of claims 1 to ~~18~~9, comprising obtaining a mammalian host cell comprising one or more vectors of claim ~~22~~12 to ~~24~~14, and cultivating the host cell.

~~29)~~19) The method according to claim ~~28~~18, further comprising recovering and purifying the antibody.

~~30)~~20) The antibody molecule of any one of claims 1 to ~~18~~9 for use in medicine.

~~31)~~21) ~~Use of an a~~Antibody molecule of any one of claims 1 to ~~18~~9 ~~for the preparation of a medicament~~ for use in the treatment of a cancerous disease selected from cancers of the hematopoietic system including leukemias, lymphomas and myelomas, cancers of the gastrointestinal tract including esophageal, gastric, colorectal, pancreatic, liver and gall bladder cancer and bile duct cancer, in particular hepatocellular carcinoma; kidney, prostate and bladder cancer; gynecological cancers including breast, ovarian, cervical and endometrial cancer; skin and head and neck cancers including malignant melanomas; pediatric cancers like Wilms' tumour, neuroblastoma and Ewing's sarcoma; brain cancers like glioblastoma; sarcomas like osteosarcoma, soft tissue sarcoma, rhabdomyosarcoma, hemangiosarcoma; lung cancer, in particular non-small cell lung cancer; mesothelioma and thyroid cancer.

~~32)~~22) The ~~use of claim 31~~antibody molecule of claim 21, wherein the medicament is to be used in combination with platinum-based chemotherapy, in particular paclitaxel/carboplatin or gemcitabine/cisplatin platinum doublet therapy, sorafenib, or a compound selected from the group of inhibitors of EGFR, VEGF, HER2-neu, AuroraB, Plk1, PI3 kinase, or mTor.

23) The antibody molecule of claim 22, wherein the inbitor of mTor is rapamycin, temsirolimus, deforolimus, or everolimus.

~~33)~~24) A pharmaceutical composition comprising an antibody molecule of any one of claims 1 to ~~18~~9 and a pharmaceutically acceptable carrier.

~~34)~~25) The pharmaceutical composition of claim ~~33~~24, further comprising one or more additional therapeutic agents selected from

a) DNA damaging agents,

b) therapeutically active compounds that inhibit signal transduction pathways or mitotic checkpoints in cancer cells,

c) antidiabetics.

~~35)~~26) The pharmaceutical composition of claim ~~34~~25, wherein said one or more compounds b) is selected from the group of inhibitors of EGFR, VEGF, HER2-neu, AuroraB, Plk1, PI3 kinase, or mTor.

~~36)~~27) The pharmaceutical composition of any one of claims ~~33~~ 24 to ~~35~~ 26 for use in the treatment of a cancerous disease selected from cancers of the hematopoietic system including leukemias, lymphomas and myelomas, cancers of the gastrointestinal tract including esophageal, gastric, colorectal, pancreatic, liver and gall bladder cancer and bile duct cancer, in particular hepatocellular carcinoma; kidney, prostate and bladder cancer; gynecological cancers including breast, ovarian, cervical and endometrial cancer; skin and head and neck cancers including malignant melanomas; pediatric cancers like Wilms' tumour, neuroblastoma and Ewing's sarcoma; brain cancers like glioblastoma; sarcomas like osteosarcoma, soft tissue sarcoma, rhabdomyosarcoma, hemangiosarcoma; lung cancer, in particular non-small cell lung cancer; mesothelioma and thyroid cancer.

~~37)~~28) The pharmaceutical composition of claim ~~36~~27, to be further used in combination with platinum-based chemotherapy, in particular paclitaxel/carboplatin or gemcitabine/cisplatin platinum doublet therapy, sorafenib, or a compound selected from the group of inhibitors of EGFR, VEGF, HER2-neu, AuroraB, Plk1, PI3 kinase, or mTor.

~~38) A method for treating a patient suffering from a cancerous disease selected from cancers of the hematopoietic system including leukemias, lymphomas and~~

~~myelomas, cancers of the gastrointestinal tract including esophageal, gastric, colorectal, pancreatic, liver and gall bladder cancer and bile duct cancer, in particular hepatocellular carcinoma; kidney, prostate and bladder cancer; gynecological cancers including breast, ovarian, cervical and endometrial cancer; skin and head and neck cancers including malignant melanomas; pediatric cancers like Wilms' tumour, neuroblastoma and Ewing's sarcoma; brain cancers like glioblastoma; sarcomas like osteosarcoma, soft tissue sarcoma, rhabdomyosarcoma, hemangiosarcoma; lung cancer, in particular non-small cell lung cancer; mesothelioma and thyroid cancer, comprising administering to said patient an effective amount of a pharmaceutical composition of any one of claims 33 to 35.~~

~~39) The method of claim 38, wherein additionally an effective amount of paclitaxel/carboplatin or gemcitabine/cisplatin, sorafenib, or a compound selected from the group of inhibitors of EGFR, VEGF, HER2-neu, AuroraB, Plk1, PI3 kinase or mTor is administered to the patient.~~

40)29) An *in vitro* method for inhibiting the binding of IGF-1 and IGF-2 to the IGF-1 receptor in a mammalian cell, comprising administering to said cell an antibody molecule of any one of claims 1 to ~~1~~89, whereby signaling mediated by the IGF-1 receptor and proliferation and anti-apoptosis mediated by IGF-1 and IGF-2 are inhibited.

41)30) An *in vitro* method for inhibiting the binding of IGF-2 to the insulin receptor IR-A in a mammalian cell, comprising administering to said cell an antibody molecule of any one of claims 1 to ~~1~~89, whereby signaling mediated by the insulin receptor IR-A is inhibited and whereby proliferation and anti-apoptosis mediated by IGF-2 is inhibited.

~~42) The method of claim 40 or 41, wherein said administering is done *in vitro*.~~

~~43)~~31) An *in vitro* method for monitoring the effectiveness of a treatment of a cancer patient with an antibody molecule that binds to IGF-1 and IGF-2, wherein said antibody molecule of any one of claims 1 to 9, wherein said method comprises

(a) measuring, in a biological sample of said patient, the level of total IGF-1,

~~(b) administering to said patient said anti-IGF antibody molecule,~~

~~(c)~~(b) measuring, in a biological sample of said patient, the level of total IGF-1, after administering to said patient said anti IGF antibody molecule wherein the amount of increase in the level of total IGF-1, compared with the level of total IGF-1 measured in step (a), indicates to which extent the patient responds to the treatment with said anti-IGF antibody molecule.

~~44) The method of claim 43, wherein said antibody molecule is an antibody molecule of any one of claims 1 to 18.~~

~~45) An anti-IGF antibody molecule, wherein said antibody molecule binds to a nonlinear epitope within IGF-1 comprising the amino acid sequences LCGAELVDALQFVCGDR (SEQ ID NO:41) and CCFRSCDLRRLEM (SEQ ID NO:42) of human IGF-1 (SEQ ID NO:43).~~

~~46) The anti-IGF antibody molecule of claim 45, wherein said antibody molecule makes contact with at least 8 amino acids within the amino acid sequence LCGAELVDALQFVCGDR (SEQ ID NO:41), and at least 10 amino acids within amino acid sequence CCFRSCDLRRLEM (SEQ ID NO:42) of human IGF-1 (SEQ ID NO:43).~~

~~47) The anti-IGF antibody molecule of claim 45 or claim 46, wherein said antibody molecule makes contact with Leu (5), Cys (6), Glu (9), Leu (10), Asp (12), Ala (13), Phe (16), Val (17), Arg (21), Cys (47), Cys (48), Phe (49), Ser (51), Cys (52), Asp (53), Leu (54), Arg (55), Leu (57), and Glu (58) of human IGF-1 (SEQ ID NO:43), as determined by X-ray crystallography.~~

~~48) The anti-IGF antibody molecule of any one of claims 45 to 47, which is the antibody molecule of any one of claims 4, 9, 10, or 17.~~