and/or a light chain amino acid sequence selected from the group consisting of SEQ. ID NOs: 37, 40 or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto or to an antibody recognizing the same epitope on the extracellular domain of AXL.

In a further embodiment the antibodies of the present invention are humanized or fully human antibodies. Humanized forms of the antibodies may be generated according to the methods known in the art such as chimerization or CDR grafting. Alternative methods for the production of humanized antibodies are well known in the art and are described in, e.g., EP-A1 0 239 400 and W090/07861. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be for example performed following the method of Winter and co-workers (Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)), by substituting CDRs or CDR sequences of non human origin for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Pat. No. 4,816,567) wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in non human antibodies.

Preferably, the present invention refers to a humanized antibody comprising a heavy chain amino acid sequence selected from the group consisting of SEQ ID NOs: 44, 46 or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto and/or a light chain amino acid sequence selected from the group consisting of SEQ. ID NOs: 43, 45 or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto or to an

Claims

1. A monoclonal antibody that binds to the extracellular domain of AXL and at least partially inhibits AXL activity; wherein the antibody comprises a heavy chain comprising at least one CDR selected from the group consisting of

(a) a CDRH1 as shown in SEQ ID NO: 22, or a CDRH1 sequence differing in 1 or 2 amino acids therefrom,

(b) a CDRH2 as shown in SEQ ID NO: 23, or a CDRH2 sequence differing in 1 or 2 amino acids therefrom, and

(c) a CDRH3 as shown in SEQ ID NO: 24, or a CDRH3 sequence differing in 1 or 2 amino acids therefrom,

and/or a light chain comprising at least one CDR selected from the group consisting of

(d) a CDRL1 as shown in SEQ ID NO: 19, or a CDRL1 sequence differing in 1 or 2 amino acids therefrom,

(e) a CDRL2 as shown in SEQ ID NO: 20, or a CDRL2 sequence differing in one or two amino acids therefrom, and

(f) a CDRL3 as shown in SEQ ID NO: 21, or a CDRL3 sequence differing in 1 or 2 amino acids therefrom, or an monoclonal antibody recognizing the same epitope on the extracellular domain of AXL.

2. The monoclonal antibody of claim 1, which reduces and/or blocks AXL-mediated signal transduction.

3. The monoclonal antibody according to anyone of claims 1-2, which reduces and/or blocks AXL phosphorylation.

4. The monoclonal antibody according to anyone of claims 1-3, which reduces and/or blocks cell proliferation.

5. The monoclonal antibody according to anyone of claims 1-4, which reduces and/or blocks angiogenesis.

6. The monoclonal antibody according to anyone of claims 1-5, which reduces and/or blocks cell migration.

7. The monoclonal antibody according to anyone of claims 1-6, which reduces and/or blocks tumor metastasis.

8. The monoclonal antibody according to anyone of claims 1-7, which reduces and/or blocks the AXL mediated anti-apoptosis.

9. The monoclonal antibody according to anyone of claims 1-8 , which reduces and/or blocks AXL mediated PI3K signaling.

10. The monoclonal antibody according to anyone of claims 1-9, which is a recombinant antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or a fragment thereof.

11. The monoclonal antibody of claim 10, which is a chimeric antibody and comprises a heavy chain amino acid sequence selected from the group consisting of SEQ ID NOs: 41, 42, or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto and/or a light chain amino acid sequence of SEQ ID NO: 40 or at least the variable domain thereof or an amino acid having a sequence identity of at least 90% thereto or an antibody recognizing the same epitope on the extracellular domain of AXL.

12. The monoclonal antibody of claim 10, which is a humanized antibody and comprises a heavy chain amino acid sequence of SEQ ID NO: 46 or

at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto and/or a light chain amino acid sequence of SEQ ID NO: 45 or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto or an antibody recognizing the same epitope on the extracellular domain of AXL.

13. The monoclonal antibody according to anyone of claims 1-12, which is a Fab fragment, a Fab' fragment, a F(ab'), fragment, a Fv fragment, a diabody, or a single chain antibody molecule.

14. The monoclonal antibody according to anyone of claims 1-13, which is of the IgG1-, IgG2-, IgG3-or IgG4-type.

15. The monoclonal antibody according to anyone of claims 1-14, which is coupled to a labelling group.

16. The monoclonal antibody according to anyone of claims 1-15, which is coupled to an effector-group.

17. The monoclonal antibody according to anyone of claims 1-16, which is a scaffold protein.

18. The monoclonal antibody according to anyone of claims 1-17, which comprises a heavy chain amino acid sequence of SEQ ID NO: 10 or at least the variable domain thereof or an amino acid having a sequence identity of at least 90% thereto and/or a light chain amino acid sequence of SEQ ID NO: 9 or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto or an antibody recognizing the same epitope on the extracellular domain of AXL.

19. An isolated nucleic acid molecule selected from the group consisting of:

(a) a nucleic acid sequence encoding an monoclonal antibody, antibody fragment or a derivative thereof of any of claims 1-18,

(b) a nucleic acid sequence as shown in SEQ ID NOs: 3, 4, 34-36,

(c) a nucleic acid complementary to any of the sequences in (a) or (b); and

(d) a nucleic acid sequence capable of hybridizing to (a), (b) or (c) under stringent conditions.

20. A vector comprising a nucleic acid sequence of claim 19.

21. The vector according to claim 20 which is an expression vector and the nucleic acid sequence is operably linked to a control sequence.

22. A host comprising the vector of claim 20 or 21.

23. The host of claim 22 which is a human, bacteria, animal, fungal, amphibian or plant cell.

24. The host of claim 22 which is a non-human transgenic animal.

25. A process of manufacturing a monoclonal antibody according to anyone of claims 1-18 comprising the step of obtaining said polypeptide from the host of claim 22, 23 or 24.

26. A pharmaceutical composition comprising an anti-AXL-antibody, preferably the monoclonal antibody of anyone of claims 1-18, the nucleic acid molecule of claim 19 the vector of claim 20 or 21, the host of claim

22, 23 or 24, or a polypeptide generated by the process of claim 25.

27. The pharmaceutical composition of claim 26 comprising pharmaceutically acceptable carriers, diluents and/or adjuvants.

28. The pharmaceutical composition according to claim 26 or 27, comprising a further active agent.

29. The pharmaceutical composition according to anyone of claims 26-28, for the diagnosis, prevention or treatment of a hyperproliferative disease.

30. The pharmaceutical composition according to anyone of claims 26-29, wherein said hyperproliferative disease is associated with AXL expression, overexpression and/or hyperactivity.

31. The pharmaceutical composition of claim 29, wherein said hyperproliferative disease is selected from the group consisting of breast cancer, lung cancer and other AXL expressing or overexpressing cancers, and formation of tumor metastases.

32. The monoclonal antibody according to anyone of claims 1-18, for the diagnosis, prevention or treatment of a hyperproliferative disease.

33. Use of the monoclonal antibody according to anyone of claims 1-18 for the manufacture of a pharmaceutical composition for the diagnosis, prevention or treatment of a hyperproliferative disease.

34. The use according to claim 32 or 33, wherein said hyperproliferative disease is a hyperproliferative disease as defined in anyone of claims 30 or 31.

35. A method for diagnosing a condition associated with the expression of AXL, comprising contacting a sample with an monoclonal antibody according to anyone of claims 1-18, and detecting the presence of AXL.

36. The method according to claim 35, wherein the condition is a hyperproliferative disease as defined in anyone of claims 30 or 31.

37. Use of the monoclonal antibody according to any one of claims 1 to 18 in the manufacture of a medicament for preventing or treating a condition associated with the expression of AXL in a patient.

38. The use according to claim 37, wherein the condition is a hyperproliferative disease as defined in anyone of claims 30 or 31.

39. The use according to claim 37 or 38, wherein the patient is a mammalian patient, particularly a human patient.

40. A kit comprising an anti-AXL-antibody, preferably a monoclonal antibody according to anyone of claims 1-18, a nucleic acid sequence according to claim 19 or a vector according to claim 20 or 21.

41. The kit according to claim 40, further comprising a further antineoplastic agent.

42. Use of an anti-AXL antibody for the manufacture of a pharmaceutical composition for the treatment of drug resistant cancer.

43. Use according to claim 42, wherein the anti-AXL antibody is a monoclonal antibody according to anyone of claims 1-18.

44. Use of an anti-AXL antibody for the manufacture of a medicament for the co-administration with an antineoplastic agent for the treatment of a

hyperproliferative disease.

45. Use according to claim 44, wherein the anti-AXL antibody is a monoclonal antibody according to any one of claims 1-18.

and/or a light chain amino acid sequence selected from the group consisting of SEQ. ID NOs: 37, 40 or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto or to an antibody recognizing the same epitope on the extracellular domain of AXL.

In a further embodiment the antibodies of the present invention are humanized or fully human antibodies. Humanized forms of the antibodies may be generated according to the methods known in the art such as chimerization or CDR grafting. Alternative methods for the production of humanized antibodies are well known in the art and are described in, e.g., EP-A1 0 239 400 and W090/07861. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be for example performed following the method of Winter and co-workers (Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)), by substituting CDRs or CDR sequences of non human origin for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Pat. No. 4,816,567) wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in non human antibodies.

Preferably, the present invention refers to a humanized antibody comprising a heavy chain amino acid sequence selected from the group consisting of SEQ ID NOs: 44, 45 or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto and/or a light chain amino acid sequence selected from the group consisting of SEQ. ID NOs: 43, 46 or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto or to an

Claims

1. A monoclonal antibody that binds to the extracellular domain of AXL and at least partially inhibits AXL activity, wherein the monoclonal antibody comprises a heavy chain amino acid sequence comprising
   (a) CDRH1 as shown in SEQ ID NO: 22,
   (b) CDRH2 as shown in SEQ ID NO: 23, and
   (c) CDRH3 as shown in SEQ ID NO: 24,
   and a light chain amino acid sequence comprising
   (d) CDRL1 as shown in SEQ ID NO: 19,
   (e) CDRL2 as shown in SEQ ID NO: 20, and
   (f) CDRL3 as shown in SEQ ID NO: 21.

2. The monoclonal antibody of claim 1, which reduces and/or blocks AXL-mediated signal transduction.

3. The monoclonal antibody according to anyone of claims 1-2, which reduces and/or blocks AXL phosphorylation.

4. The monoclonal antibody according to anyone of claims 1-3, which reduces and/or blocks cell proliferation.

5. The monoclonal antibody according to anyone of claims 1-4, which reduces and/or blocks angiogenesis.

6. The monoclonal antibody according to anyone of claims 1-5, which reduces and/or blocks cell migration.

7. The monoclonal antibody according to anyone of claims 1-6, which

reduces and/or blocks tumor metastasis.

8. The monoclonal antibody according to anyone of claims 1-7, which reduces and/or blocks the AXL mediated anti-apoptosis.

9. The monoclonal antibody according to anyone of claims 1-8, which reduces and/or blocks AXL mediated PI3K signaling.

10. The monoclonal antibody according to anyone of claims 1-9, which is a recombinant antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or a fragment thereof.

11. The monoclonal antibody of claim 10, which is a chimeric antibody and comprises a heavy chain amino acid sequence selected from the group consisting of SEQ ID NOs: 41, 42, or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto and/or a light chain amino acid sequence of SEQ ID NO: 40 or at least the variable domain thereof or an amino acid having a sequence identity of at least 90% thereto or an antibody recognizing the same epitope on the extracellular domain of AXL.

12. The monoclonal antibody of claim 10, which is a humanized antibody and comprises a light chain amino acid sequence of SEQ ID NO: 46 or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto and/or a heavy chain amino acid sequence of SEQ ID NO: 45 or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto or an antibody recognizing the same epitope on the extracellular domain of AXL.

13. The monoclonal antibody according to anyone of claims 1-12, which is a

Fab fragment, a Fab' fragment, a F(ab'), fragment, a Fv fragment, a diabody, or a single chain antibody molecule.

14. The monoclonal antibody according to anyone of claims 1-13, which is of the IgG1-, IgG2-, IgG3-or IgG4-type.

15. The monoclonal antibody according to anyone of claims 1-14, which is coupled to a labelling group.

16. The monoclonal antibody according to anyone of claims 1-15, which is coupled to an effector-group.

17. The monoclonal antibody according to anyone of claims 1-16, which is a scaffold protein.

18. The monoclonal antibody according to anyone of claims 1-17, which comprises a heavy chain amino acid sequence of SEQ ID NO: 10 or at least the variable domain thereof or an amino acid having a sequence identity of at least 90% thereto and/or a light chain amino acid sequence of SEQ ID NO: 9 or at least the variable domain thereof or an amino acid sequence having a sequence identity of at least 90% thereto or an antibody recognizing the same epitope on the extracellular domain of AXL.

19. An isolated nucleic acid molecule selected from the group consisting of:

(a) a nucleic acid sequence encoding a monoclonal antibody, antibody fragment or a derivative thereof of any of claims 1-18,

(b) a nucleic acid sequence as shown in SEQ ID NOs: 3, 4, 34-36, and

(c) a nucleic acid complementary to any of the sequences in (a) or (b).

20. A vector comprising a nucleic acid sequence of claim 19.

21. The vector according to claim 20 which is an expression vector and the nucleic acid sequence is operably linked to a control sequence.

22. A host comprising the vector of claim 20 or 21.

23. The host of claim 22 which is a human, bacteria, animal, fungal, amphibian or plant cell.

24. The host of claim 22 which is a non-human transgenic animal.

25. A process of manufacturing a monoclonal antibody according to anyone of claims 1-18 comprising the step of obtaining said polypeptide from the host of claim 22, 23 or 24.

26. A pharmaceutical composition comprising the monoclonal antibody of anyone of claims 1-18, the nucleic acid molecule of claim 19, the vector of claim 20 or 21, the host of claim 22, 23 or 24, or a polypeptide generated by the process of claim 25.

27. The pharmaceutical composition of claim 26 comprising pharmaceutically acceptable carriers, diluents and/or adjuvants.

28. The pharmaceutical composition according to claim 26 or 27, comprising a further active agent.

29. The pharmaceutical composition according to anyone of claims 26-28, for the diagnosis, prevention or treatment of a hyperproliferative disease.

30. The pharmaceutical composition according to claim 29, wherein said hyperproliferative disease is associated with AXL expression, overexpression and/or hyperactivity.

31. The pharmaceutical composition of claim 29, wherein said hyperproliferative disease is selected from the group consisting of breast cancer, lung cancer and other AXL expressing or overexpressing cancers, and formation of tumor metastases.

32. The monoclonal antibody according to anyone of claims 1-18, for the diagnosis, prevention or treatment of a hyperproliferative disease.

33. Use of the monoclonal antibody according to anyone of claims 1-18 for the manufacture of a pharmaceutical composition for the diagnosis, prevention or treatment of a hyperproliferative disease.

34. The monoclonal antibody according to claim 32 or the use according to claim 33, wherein said hyperproliferative disease is a hyperproliferative disease as defined in anyone of claims 30 or 31.

35. A method for diagnosing a condition associated with the expression of AXL, comprising contacting a sample with a monoclonal antibody according to anyone of claims 1-18, and detecting the presence of AXL.

36. The method according to claim 35, wherein the condition is a hyperproliferative disease as defined in anyone of claims 30 or 31.

37. Use of the monoclonal antibody according to any one of claims 1 to 18 in the manufacture of a medicament for preventing or treating a condition associated with the expression of AXL in a patient.

38. The use according to claim 37, wherein the condition is a hyperproliferative disease as defined in anyone of claims 30 or 31.

39. The use according to claim 37 or 38, wherein the patient is a mammalian patient, particularly a human patient.

40. A kit comprising a monoclonal antibody according to anyone of claims 1-18, a nucleic acid sequence according to claim 19 or a vector according to claim 20 or 21.

41. The kit according to claim 40, further comprising a further antineoplastic agent.

42. Use of a monoclonal antibody according to anyone of claims 1-18 for the manufacture of a pharmaceutical composition for the treatment of drug resistant cancer.

43. Use of a monoclonal antibody of anyone of claims 1-18 for the manufacture of a medicament for the co-administration with an antineoplastic agent for the treatment of a hyperproliferative disease.