rendering them unsuitable for therapeutic administration.

Thus in light of the therapeutic potential of AXL there is a high need for monoclonal AXL antibodies, antibody fragments or derivatives thereof that effectively and specifically block AXL mediated signal transduction and which are suitable for therapeutic treatment.

Summary of Invention

In one aspect, there is provided 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: 16,

(b) a CDRH2 as shown in SEQ ID NO: 17, and

(c) a CDRH3 as shown in SEQ ID NO: 18,

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: 13,

(e) a CDRL2 as shown in SEQ ID NO: 14, and

(f) a CDRL3 as shown in SEQ ID NO: 15, or a monoclonal antibody recognizing the same epitope on the extracellular domain of AXL.

In another aspect, there is provided an isolated nucleic acid molecule selected from the group consisting of:

(a) a nucleic acid sequence encoding a monoclonal antibody as described herein, antibody fragment or a derivative thereof of the present invention,

(b) a nucleic acid sequence as shown in SEQ ID Nos: 1-2, 31-33;

(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.

In a further aspect, there is provided a vector comprising a nucleic acid sequence of the present invention.

In a further aspect, there is provided a host comprising the vector of the present invention.

In a further aspect, there is provided a process of manufacturing a monoclonal antibody of the present invention, comprising the step of obtaining said polypeptide from the host of the present invention.

In yet a further aspect, there is provided a pharmaceutical composition comprising an anti-AXL-antibody, preferably the monoclonal antibody of the present invention, the nucleic acid molecule of the present invention, the vector of the present invention, the host of the present invention, or a polypeptide generated by the process of the present invention.

In another aspect, there is provided the monoclonal antibody of the present invention, for the diagnosis, prevention or treatment of a hyperproliferative disease.

In a further aspect, there is provided the use of the monoclonal antibody of the present invention, for the manufacture of a pharmaceutical composition for the diagnosis, prevention or treatment of a hyperproliferative disease.

In a further aspect, there is provided a method for diagnosing a condition associated with the expression of AXL, comprising contacting a sample with a monoclonal antibody of the present invention, and detecting the presence of AXL.

In yet a further aspect, there is provided the use of the monoclonal antibody of the present invention, in the manufacture of a medicament for preventing or treating a condition associated with the expression of AXL in a patient, wherein the condition is a hyperproliferative disease as defined herein.

In another aspect, there is provided a kit comprising an anti-AXL-antibody, preferably a monoclonal antibody of the present invention, a nucleic acid sequence of the present invention or a vector of the present invention.

In another aspect, there is provided the use of an anti-AXL antibody for the manufacture of a pharmaceutical composition for the treatment of drug resistant cancer.

In a further aspect, there is provided the 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 as defined herein.

Detailed Description

Accordingly a first aspect of the present invention relates to a monoclonal antibody including a fragment or derivative thereof that binds to the extracellular domain of AXL, particularly of human AXL, and at least partially inhibits AXL activity.

Preferably the antibody of the present invention further possesses at least one or more of the following properties: the ability to reduce or block AXL-mediated signal transduction, the ability to reduce or block AXL phosphorylation, the ability to reduce or block cell proliferation, the ability to reduce or block angiogenesis, the ability to reduce or block cell migration, the ability to reduce or block tumor metastasis, the ability to reduce or block AXL mediated PI3K signaling and the ability to reduce or block AXL mediated anti-apoptosis, thereby increasing for example the sensitivity of a cell against treatment with an antineoplastic agent. Moreover the antibodies of the present invention may exhibit high specificity for AXL, particularly human AXL and do not significantly recognize other Tyro-3 family members, e.g. MER and/or SKY and/or mammalian non-primate AXL, such as murine AXL. Antibody specificity may be determined by measurements of cross-reactivity as described in the Examples.

The term "activity" refers to the biological function of AXL, which influences the phenotype of a cell, in particular but not limited to cancer phenotypes such as evasion of apoptosis, self sufficiency in growth signals, cell proliferation, tissue invasion and/or metastasis, insensitivity to anti-growth signals (anti-apoptosis) and/or sustained angiogenesis.

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 ~~34~~ 30 or ~~35~~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, wherein the condition is a hyperproliferative disease as defined in any one of claims 30 or 31.

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

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

~~40.~~39. 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.~~40. The kit according to claim ~~40~~39, further comprising a further antineoplastic agent.

~~42.~~41. Use of an anti-AXL antibody for the manufacture of a pharmaceutical composition for the treatment of drug resistant cancer.

~~43.~~42. Use according to claim ~~42~~41, wherein the anti-AXL antibody is a monoclonal antibody according to anyone of claims 1-18.

~~44.~~43. 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 as defined in anyone of claim 30 or 31.

~~45.~~44. Use according to claim ~~44~~43, wherein the anti-AXL antibody is a monoclonal antibody according to any one of claims 1-18.