CLAIMS

1. Method for selecting a compound for the prevention or the treatment of cancer, wherein said method comprises the following steps of:

a) having a medium containing netrin-1, or a fragment thereof, and a netrin-1 receptor, or a fragment thereof, wherein:

- said netrin-1, or a fragment thereof, and said netrin-1 receptor, or a fragment thereof, is able to specifically interact together to form a binding pair, and/or

- said netrin-1, or a fragment thereof, is able to induce the dimerization or multimerization of said netrin-1 receptor, or a fragment thereof, particularly the intracellular domain of said netrin-1 receptor;

b) contacting said medium with the compound to be tested;

c) - measuring the inhibition of the interaction between netrin-1, or a fragment thereof, and said netrin-1 receptor, or a fragment thereof, and/or

- determine whether said compound inhibit the dimerization or multimerization of said netrin-1 receptor, or a fragment thereof, particularly the dimerization of the intracellular domain of said netrin-1 receptor; and

d) selecting said compound if:

- the measuring in step c) demonstrates a significantly inhibition of the interaction between netrin-1, or a fragment thereof, and netrin-1 receptor, or a fragment thereof, in presence of said compound, and/or

- the determination in step c) demonstrates a significantly inhibition of the dimerization or multimerization of said netrin-1 receptor, or a fragment thereof, in presence of said compound, particularly the dimerization of the intracellular domain of said netrin-1 receptor.

2. The method according to claim 1, wherein said cancer to be prevent or treated is a cancer wherein tumoral cells express or overexpress netrin-1.

3. The method according to claim 1 or 2, wherein said cancer to be prevent or treated is selected from the group consisting of breast cancer, colorectal cancer, lung cancer, neuroblastoma, glioma, acute myeloid leukemia, sarcoma, melanoma, ovarian adenocarcinoma, renal adenocarcinoma pancreatic adenocarcinoma, uterus

adenocarcinoma, stomac adenocarcinoma, kidney adenocarcinoma and rectal adenocarcinoma.

4. The method according to claims 1 to 3, wherein said cancer to be prevent or treated is a metastatic cancer or an aggressive cancer.

5. The method according to claims 1 to 4, wherein at step a) said netrin-1 receptor is selected from the group of DCC, UNC5H (particularly UNC5H1, UNC5H2 and UNC5H3), neogenin and the adenosine A2b.

6. The method according to claim 5, wherein at step a) said netrin-1 receptor is selected from the group of DCC, UNC5H1, UNC5H2 and UNC5H3.

7. The method according to claims 1 to 6, wherein at step a):

- said netrin-1 receptor fragment comprises or is the extracellular domain of the netrin-1 receptor, or part thereof able to interact with netrin-1; and/or
- said netrin-1 receptor fragment comprises or is the intracellular domain of the netrin-1 receptor, or part thereof able to dimerize or multimerize in presence of netrin-1.

8. The method according to claims 1 to 7, wherein at step a) said netrin-1 or/and said netrin 1 receptor are from mammal, particularly from mouse, rat or human.

9. The method according to claims 1 to 8, wherein at step a) said netrin-1 is from chicken.

10. The method according to claims 1 to 9, wherein said netrin-1 or/and said netrin-1 receptor and/or the compound to be tested is labelled by a marker able to be directly or indirectly measured.

11. The method according to claims 1 to 10, wherein at step c):

- the measure of the inhibition of the interaction between netrin-1, or a fragment thereof, and said netrin-1 receptor, or a fragment thereof, is carried out by immunoassay (particularly by ELISA or by Immunoradiometric Assay (IRMA)), by Scintillation Proximity Assay (SPA) or by Fluorescence Resonance Energy Transfer (FRET); and/or
- the dimerization or multimerization, or its inhibition, of said netrin-1 receptor, or fragment thereof, particularly the intracellular domain, is carried out by immunoprecipitation or FRET.

12. The method according to claims 1 to 11, wherein at step a) said medium contains cells which express at their surface membrane an endogenous netrin-1 receptor or

a recombinant netrin-1 receptor, particularly at least the extracellular domain of a recombinant netrin-1 receptor.

13. The method according to claim 12, wherein at step a) said medium contains cells which express recombinant netrin-1 receptor.

14. The method according to claim 12, wherein at step a) said medium contains tumoral cells which express endogenously said netrin-1 receptor at their membrane surface and which express or overexpress netrin-1, and wherein at step c) the inhibition of the interaction between netrin-1 and its netrin-1 receptor in presence of the compound to be tested, is measured by the apoptosis or cells death induced by the presence of the compound to be tested.

15. The method according to claim 14, wherein at step a) said medium contains metastatic tumoral cells, particularly cells selected from the group consisting of 4T1 cells, CAL51 cells, T47D cells, SKBR7 cells, IMR32 cells, GL26 cells and H358 cells.

16. A method according to claims 1 to 15 for selecting a compound for the prevention or the treatment of cancer, wherein said method comprises the following steps of:

a) having a medium containing a mammal cell expressing an endogenous or a recombinant netrin-1 receptor, or a fragment thereof comprising at least its intracellular domain, preferably a tumor cell, more preferably a cell presenting dimerization or multimerization of its netrin-1 receptor intracellular domain or a cell wherein its netrin-1 receptor intracellular domain is able to dimerize or multimerize in presence of netrin-1;

b) contacting said medium with the compound to be tested, optionally the medium further containing netrin-1, or a fragment thereof able to interact with the extracellular domain of the netrin-1 receptor;

c) determine whether the dimerization or multimerization of said netrin-1 receptor intracellular domain is inhibited in presence of said compound to be tested;

d) optionally, determine whether the presence of the compound to be tested induces the cell death of said mammal cell; and

e) selecting said compound if the determination in step c) demonstrates a significantly inhibition of the dimerization or multimerization of the intracellular domain of said netrin-1

receptor and/or if the determination in step d) demonstrates the cell death of said mammal cell.

17. An in vitro method for predicting the presence of a metastatic or an aggressive cancer in a patient having a primary tumor from a biopsy of said patient containing primary tumors cells, said method comprising the following step of:

(a) measuring of the netrin-1 expression level in said biopsy.

18. The method according to claim 17, wherein an increase of the netrin-1 expression level in said biopsy, compared with expression of netrin-1 in a non-metastatic primary tumor biopsies or in a non-aggressive cancer biopsies is significant of the presence of a metastatic cancer or an aggressive cancer.

19. The method according to claims 17 and 18, wherein a ratio superior to 2 between netrin-1 expression in the biopsy to be tested and in the non-metastatic reference biopsy is significant of the presence of a metastatic cancer.

20. A method for determining *in vitro* the efficiency of an anti-cancer treatment for a patient or for *in vitro* selecting patients who respond to a specific anti-cancer treatment, said method comprising the following step of:

(a) obtaining a primary tumor biopsy of said treated patient; and

(b) measuring of the netrin-1 expression level in said biopsy,

wherein the efficiency of said anti-cancer treatment is correlated with the decrease of the amount of the netrin-1 expression level measured in said biopsy, or

wherein the selected patients who respond to a specific anti-cancer treatment are patients where the amount of the netrin-1 expression level measured in their biopsy has been decreased after said specific treatment.

21. A method according to claim 20, wherein said cancer induced an overexpression of netrin-1 and/or is a metastatic or an aggressive cancer.

22. The method according to claims 17 to 21, wherein the measured netrin-1 expression product is the RNA encoding netrin-1, particularly measured by a quantitative real time reverse PCR method.

23. The method according to claims 17 to 21, wherein the expression level of netrin-1 which is measured is the measuring of the netrin-1 protein level, particularly by a method using specific antibodies able to specifically recognize said netrin-1 protein.

24. The method according to claims 17 to 23, wherein the primary tumor is a primary tumor of a cancer selected from the group consisting of breast cancer, colorectal cancer, lung cancer, neuroblastoma, glioma, acute myeloid leukemia, sarcoma, melanoma, ovarian adenocarcinoma, renal adenocarcinoma pancreatic adenocarcinoma, uterus adenocarcinoma, stomac adenocarcinoma, kidney adenocarcinoma and rectal adenocarcinoma.

25. Kit for the selection of a compound for the prevention or the treatment of cancer, wherein said kit comprises:

- a netrin-1 receptor protein, or a fragment thereof able to specifically interact with the netrin-1 protein to form a binding pair, preferably recombinant protein; and

- netrin-1 protein, or a fragment thereof able to specifically interact with said netrin-1 receptor protein to form a binding pair, preferably recombinant protein.

26. Kit for the selection of a compound for the prevention or the treatment of cancer, wherein said kit comprises:

- tumoral cells which express netrin-1 receptor and which express or overexpress netrin-1, particularly cells from tumoral cell line, preferably selected from the group consisting of 4T1 cells, CAL51 cells, T47D cells, SKBR7 cells, IMR32 cells, GL26 cells and H358 cells; and, optionally,

- netrin-1 protein, or a fragment thereof able to specifically interact with said netrin-1 receptor protein to form a binding pair, preferably a recombinant netrin-1 protein.

27. A compound selected from the group consisting of:

- a compound selected by the method of claims 1 to 15;

- a compound comprising an extracellular domain of netrin-1 receptor or fragment thereof able to specifically inhibit the interaction between the netrin-1 and said netrin-1 receptor, and/or able to inhibit the dimerization or multimerization of said netrin-1 receptor, or a fragment thereof, particularly the intracellular domain of said netrin-1 receptor; and

- a monoclonal or polyclonal antibody directed specifically against netrin-1 or netrin-1 receptor, particularly directed to the extracellular domain of said netrin-1 receptor or to the netrin-1 fragment able to interact with the extracellular domain of said netrin-1 receptor,

as a medicament.

28. A compound according to claim 27, wherein said extracellular domain of netrin-1 receptor or fragment thereof is selected from the group of DCC, UNC5H (particularly UNC5H1, UNC5H2 and UNC5H3), neogenin and the adenosine A2b.

29. A compound according to claim 27 or 28, wherein said compound comprising an extracellular domain of netrin-1 receptor is from DCC, preferably said compound is DCC-EC-Fc or DCC-5Fbn.

30. Method of treatment for inducing the apoptosis or the cell death of tumor cells which have acquired the selective advantage to escape netrin-1 dependence receptors induced apoptosis, preferably by elevated netrin-1 level, in a patient comprising administering a compound able to inhibit this selective advantage in a tumor cell in said patient in need thereof.

31. Method for the prevention or for the treatment of cancer in a patient comprising administering a compound according to claims 27 to 29 in said patient in need thereof.

32. Use of a compound according to claims 27 to 29 for the manufacture of a medicament for the prevention or the treatment of cancer in mammals, including man.

33. The method or the use according to claim 31 or 32, characterized in that said cancer is a metastatic or an aggressive cancer.

34. The method or the use according to claims 30 to 32, characterized in that said cancer selected from the group consisting of breast cancer, colorectal cancer, lung cancer, neuroblastoma, glioma, acute myeloid leukemia, sarcoma, melanoma, ovarian adenocarcinoma, renal adenocarcinoma pancreatic adenocarcinoma, uterus adenocarcinoma, stomac adenocarcinoma, kidney adenocarcinoma and rectal adenocarcinoma.

35. The method or the use according to claims 29 to 34, characterized in that the primary tumor cells of said cancer express or overexpress netrin-1.

36. Use of the level of netrin-1 expression as a marker for the identification of a metastatic or an aggressive cancer in a patient.

37. Use according to claim 36, wherein said metastatic or aggressive cancer is selected from the group consisting of breast cancer, colorectal cancer, lung cancer, neuroblastoma, glioma, acute myeloid leukemia, sarcoma, melanoma, ovarian

adenocarcinoma, renal adenocarcinoma pancreatic adenocarcinoma, uterus adenocarcinoma, stomac adenocarcinoma, kidney adenocarcinoma and rectal adenocarcinoma.

CLAIMS

1. Method for selecting a compound for the prevention or the treatment of cancer, said cancer to be prevented or treated being selected from the group consisting of breast cancer, lung cancer, neuroblastoma, glioma, leukemia, sarcoma, melanoma and adenocarcinoma, wherein said cancer to be prevented or treated is a cancer wherein tumoral cells express or overexpress netrin-1, wherein said method comprises the following steps of:

a) having a medium containing netrin-1, or a fragment thereof, and a netrin-1 receptor, or a fragment thereof, wherein:

- said netrin-1, or a fragment thereof, and said netrin-1 receptor, or a fragment thereof, is able to specifically interact together to form a binding pair, and/or

- said netrin-1, or a fragment thereof, is able to induce the dimerization or multimerization of the intracellular domain of said netrin-1 receptor;

b) contacting said medium with the compound to be tested;

c) - measuring the inhibition of the interaction between netrin-1, or a fragment thereof, and said netrin-1 receptor, or a fragment thereof, and/or

- determining whether said compound inhibits the dimerization or multimerization of said netrin-1 receptor, or a fragment thereof, particularly the dimerization of the intracellular domain of said netrin-1 receptor; and

d) selecting said compound if:

- the measuring in step c) demonstrates a significant inhibition of the interaction between netrin-1, or a fragment thereof, and netrin-1 receptor, or a fragment thereof, in presence of said compound, and/or

- the determination in step c) demonstrates a significant inhibition of the dimerization or multimerization, in presence of said compound, of the intracellular domain of said netrin-1 receptor.

2. The method according to claim 1, wherein said adenocarcinoma to be prevented or treated is selected from the group consisting of ovarian adenocarcinoma, renal adenocarcinoma, pancreatic adenocarcinoma, uterus adenocarcinoma, stomac adenocarcinoma, kidney adenocarcinoma and rectal adenocarcinoma.

3. The method according to claim 1 or 2, wherein said cancer to be prevented or treated is a metastatic cancer.

4. The method according to claims 1 to 3, wherein at step a) said netrin-1 receptor is selected from the group of Deleted in Colorectal Cancer (DCC), Unc-5 homolog (UNC5H), neogenin and the adenosine A2b receptors.

5. The method according to claim 4, wherein at step a) said netrin-1 receptor is selected from the group of DCC, UNC5H1, UNC5H2 and UNC5H3.

6. The method according to claims 1 to 5, wherein at step a):

- said netrin-1 receptor fragment comprises or is the extracellular domain of the netrin-1 receptor, or part thereof able to bind to netrin-1; and/or
- said netrin-1 receptor fragment comprises or is the intracellular domain of the netrin-1 receptor, or part thereof able to dimerize or multimerize in presence of netrin-1.

7. The method according to claims 1 to 6, wherein at step a) said netrin-1 or/and said netrin 1 receptor are from mammal.

8. The method according to claims 1 to 7, wherein at step a) said netrin-1 is from chicken.

9. The method according to claims 1 to 8, wherein said netrin-1 or/and said netrin-1 receptor and/or the compound to be tested is labeled by a marker able to be directly or indirectly measured.

10. The method according to claims 1 to 9, wherein at step c):

- the measure of the inhibition of the interaction between netrin-1, or a fragment thereof, and said netrin-1 receptor, or a fragment thereof, is carried out by immunoassay (particularly by Enzyme-linked Immunosorbent Assay (ELISA) or by Immunoradiometric Assay (IRMA)), by Scintillation Proximity Assay (SPA) or by Fluorescence Resonance Energy Transfer (FRET); and/or
- the dimerization or multimerization, or its inhibition, of said netrin-1 receptor, or fragment thereof, particularly the intracellular domain, is carried out by immunoprecipitation or FRET.

11. The method according to claims 1 to 10, wherein at step a) said medium contains cells which express at their surface membrane an endogenous netrin-1 receptor or

a recombinant netrin-1 receptor, particularly at least the extracellular domain of a recombinant netrin-1 receptor.

12. The method according to claim 11, wherein at step a) said medium contains cells which express recombinant netrin-1 receptor.

13. The method according to claim 11, wherein at step a) said medium contains tumoral cells which express endogenously said netrin-1 receptor at their membrane surface and which express or overexpress netrin-1, and wherein at step c) the inhibition of the interaction between netrin-1 and its netrin-1 receptor in presence of the compound to be tested, is measured by the apoptosis or cells death induced by the presence of the compound to be tested.

14. The method according to claim 13, wherein at step a) said medium contains metastatic tumoral cells.

15. A method according to claims 1 to 14 for selecting a compound for the prevention or the treatment of cancer, wherein said method comprises the following steps of:

a) having a medium containing a mammal cell expressing an endogenous or a recombinant netrin-1 receptor, or a fragment thereof comprising at least its intracellular domain;

b) contacting said medium with the compound to be tested;

c) determining whether the dimerization or multimerization of said netrin-1 receptor intracellular domain is inhibited in presence of said compound to be tested; and

d) selecting said compound if the determination in step c) demonstrates a significant inhibition of the dimerization or multimerization of the intracellular domain of said netrin-1 receptor.

16. The method according to claim 15, wherein said cell of step (a) is a tumor cell.

17. The method according to claim 15, wherein said cell of step (a) is a cell presenting dimerization or multimerization of its netrin-1 receptor intracellular domain or a cell wherein its netrin-1 receptor intracellular domain is able to dimerize or multimerize in presence of netrin-1.

18. The method according to any one of claims 15 to 17, wherein at step (b) the medium further containing netrin-1, or a fragment thereof able to bind to the extracellular domain of the netrin-1 receptor.

19. The method according to any one of claims 15 to 18, comprising further determining whether the presence of the compound to be tested induces the cell death of said mammal cell; and step (d) comprises the determination of the cell death of said mammal cell.

20. An in vitro method for predicting the presence of a metastatic or an aggressive cancer in a patient having a primary tumor from a biopsy of said patient containing primary tumors cells, said cancer being selected from the group consisting of breast cancer, lung cancer, neuroblastoma, glioma, leukemia, sarcoma, melanoma and adenocarcinoma, wherein said cancer to be prevented or treated is a cancer wherein tumoral cells express or overexpress netrin-1, comprising the following step of:

(a) measuring of a netrin-1 expression product level in said biopsy, wherein said product is (i) RNA encoding netrin-1 or (ii) netrin-1 protein; and

(b) comparing said expression product level with expression of netrin-1 expression product level in a non-metastatic primary tumor biopsy or in a non-aggressive cancer biopsy ;

wherein an increase with a ratio superior to 2 between netrin-1 expression product levels in the biopsy to be tested and in the non-metastatic or non-aggressive reference biopsy is significant of the presence of a metastatic cancer or an aggressive cancer.

21. A method for determining *in vitro* the efficiency of an anti-cancer treatment for a patient or for *in vitro* selecting patients who respond to a specific anti-cancer treatment, said cancer being selected from the group consisting of breast cancer, lung cancer, neuroblastoma, glioma, leukemia, sarcoma, melanoma and adenocarcinoma, wherein said cancer to be prevented or treated is a cancer wherein tumoral cells express or overexpress netrin-1, said method comprising the following step of:

- measuring of a netrin-1 expression product level in a biopsy of said patient, wherein said product is (i) RNA encoding netrin-1 or (ii) netrin-1 protein;

wherein the efficiency of said anti-cancer treatment is correlated with the decrease by a ratio of at least 2 of the amount of the netrin-1 expression product level measured in said biopsy, or

wherein the selected patients who respond to a specific anti-cancer treatment are patients where the amount of the netrin-1 expression product level measured in their biopsy has been decreased by a ratio of at least 2 after said specific treatment.

22. A method according to claim 21, wherein said cancer induced an overexpression of netrin-1 and/or is a metastatic cancer.

23. The method according to claims 20 to 22, wherein said RNA encoding netrin-1 is measured by a quantitative real time reverse polymerase chain reaction (PCR) method.

24. The method according to claims 20 to 22, wherein said netrin-1 protein is measured using specific antibodies able to specifically recognize said netrin-1 protein.

25. The method according to claims 20 to 24, wherein the primary tumor is a primary tumor of a cancer selected from the group consisting of breast cancer, lung cancer, neuroblastoma, glioma, leukemia, sarcoma, melanoma and adenocarcinoma.

26. The method according to claim 25, wherein said adenocarcinoma is selected from the group consisting of ovarian adenocarcinoma, renal adenocarcinoma, pancreatic adenocarcinoma, uterus adenocarcinoma, stomac adenocarcinoma, kidney adenocarcinoma and rectal adenocarcinoma.

27. Use for the selection of a compound for the prevention or the treatment of cancer, said cancer being selected from the group consisting of breast cancer, lung cancer, neuroblastoma, glioma, leukemia, sarcoma, melanoma and adenocarcinoma, of a kit comprising tumoral cells which express netrin-1 receptor and express or overexpress netrin-1.

28. Use according to claim 27, wherein the tumoral cells are cells from a tumoral cell line.

29. Use according to claim 27 or 28, further comprising a netrin-1 protein, or a fragment thereof able to specifically interact with said netrin-1 receptor protein to form a binding pair.

30. A compound selected from the group consisting of:

- a compound comprising an extracellular domain of netrin-1 receptor or fragment thereof able to specifically inhibit the interaction between the netrin-1 and said netrin-1 receptor, and/or able to inhibit the dimerization or multimerization of the intracellular domain of said netrin-1 receptor; and

- a monoclonal or polyclonal antibody directed specifically against netrin-1 or the extracellular domain of netrin-1 receptor or to a netrin-1 fragment able to interact with the extracellular domain of said netrin-1 receptor,

for use in an in vivo method to prevent or treat breast cancer, lung cancer, neuroblastoma, glioma, leukemia, sarcoma, melanoma and adenocarcinoma.

31. A compound for the use according to claim 30, wherein said extracellular domain of netrin-1 receptor or fragment thereof is selected from the group of DCC, UNC5H , neogenin and the adenosine A2b.

32. A compound for the use according to claim 30 or 31, wherein said compound comprising an extracellular domain of netrin-1 receptor is from DCC.

33. A compound for the use according to claim 32, wherein said compound is DCC-EC-Fc or DCC-5Fbn.

34. A compound for the use according to any one of claims 30 to 33, for use in a method to prevent or treat a cancer wherein tumoral cells express or overexpress netrin-1.

35. The compound according to claims 30 to 34 or an antisense or iRNA (interfering RNA) oligonucleotide which is specific and complementary to the nucleic acid encoding netrin-1 protein for use in an in vivo method to treat or prevent breast cancer in mammals, including man, said cancer being selected from the group consisting of breast cancer, lung cancer, neuroblastoma, glioma, leukemia, sarcoma, melanoma and adenocarcinoma, wherein said cancer to be prevented or treated is a cancer wherein tumoral cells express or overexpress netrin-1.

36. The use of the compound according to claim 35, characterized in that said cancer is a metastatic cancer.

37. The use of the compound according to claim 35 or 33, characterized in that said adenocarcinoma is selected from the group consisting of ovarian adenocarcinoma, renal adenocarcinoma, pancreatic adenocarcinoma, uterus adenocarcinoma, stomac adenocarcinoma, kidney adenocarcinoma and rectal adenocarcinoma.

38. The use of the compound according to claims 35 to 37, characterized in that the primary tumor cells of said cancer express or overexpress netrin-1.