

However, these antibodies are only intended to be used for therapeutic application. Indeed, none of them may be used in immunohistochemistry (IHC) staining and thus have diagnostic application.

Monoclonal antibodies usable in IHC are highly valuable in clinic. In particular, in the cancer field mAb validated for IHC are used to diagnose a cancer as benign or malignant, determine the stage and grade of a tumor, and identify the cell type and origin of a metastasis to find the site of the primary tumor. IHC validated mAb are also widely used to predict therapeutic response notably in breast carcinoma.

In this context, mAb that can be used for both therapeutic and diagnostic (*i.e.*, target detection) purposes are of crucial interest in clinic because they allow to determine patient eligibility to the treatment. Furthermore, the use of a unique and same antibody for diagnosis, prognosis and treatment is of considerable interest in terms of reliability and cost development.

Thus, there remains a need to develop an anti-Nectin-4 being usable in diagnostic application through IHC assays, while having excellent therapeutic properties.

15 SUMMARY

The present disclosure relates to antibodies having specificity for Nectin-4 and uses thereof.

In particular, it is disclosed herein an anti-Nectin-4 antibody, which selectively binds to Nectin-4 in a biological sample in an IHC assay. More specifically, said antibody selectively binds to Nectin-4 in a tissue sample section, notably a fixed tissue sample and more particularly a Formaldehyde Fixed Paraffin Embedded (FFPE) tissue sample. Such antibody is thus usable for diagnosis and/or prognosis purposes.

In some examples, the anti-Nectin-4 antibody of the present disclosure binds Nectin-4, notably the human Nectin-4 of SEQ ID NO:1, with an apparent affinity-binding constant value (K_D) of less than 10 $\mu\text{g/mL}$, notably less 1 $\mu\text{g/mL}$, less than 100 ng/mL , less than 10 ng/mL or less than 5 ng/mL . Such antibody is thus typically usable for therapeutic application.

In specific examples, an anti-Nectin-4 mAb according to the present disclosure competes for binding to Nectin-4 with the following reference murine antibody mAb 5A12.2 as obtainable by the hybridoma deposited at the CNCM under deposit number **CNCM I-5407**.

In specific examples, an anti-Nectin-4 antibody according to the present disclosure comprises a heavy chain and a light chain comprising the 6 CDRs of the antibody mAb 5A12.2, said mAb 5A12.2 being obtainable by the hybridoma deposited at the CNCM under deposit number **CNCM I-5407**. Typically, the anti-Nectin-4 antibody of the present disclosure comprises:

- a HCDR1 of SEQ ID NO:2, a HCDR2 of SEQ ID NO:3, a HCDR3 of SEQ ID NO:4, a LCDR1 of SEQ ID NO:5, a LCDR2 of SEQ ID NO:6 and a LCDR3 of SEQ ID NO:7;
- a variable heavy chain (VH) domain and a variable light chain domain having at least 90 % identity with the heavy chain and light chain of SEQ ID NO:8 and 9 respectively; and/or
- a variable heavy chain (VH) domain and a variable light chain of SEQ ID NO:8 and 9 respectively.

An aspect of the present disclosure relates to an antibody having specificity for human Nectin-4 and comprising a HCDR1 of SEQ ID NO:2, a HCDR2 of SEQ ID NO:3, a HCDR3 of SEQ ID NO:4, a LCDR1 of SEQ ID NO:5, a LCDR2 of SEQ ID NO:6 and a LCDR3 of SEQ ID NO:7.

In specific examples, said anti-Nectin-4 antibody is a human, chimeric or humanized antibody.

In some examples of the present disclosure, the anti-Nectin-4 antibody is conjugated to a cytotoxic moiety.

Another example of the present disclosure relates to a nucleic acid molecule, which encodes a heavy chain and/or a light chain of any of the anti-Nectin-4 antibodies as described above.

Another aspect of the present disclosure relates to a nucleic acid molecule, which encodes a heavy chain and a light chain of the anti-Nectin-4 antibody as disclosed herein.

The disclosure also pertains to a host cell comprising such nucleic acids, in particular for use in the manufacturing of any one of the anti-Nectin-4 antibodies as described above.

Another aspect of the present disclosure relates to a host cell comprising the nucleic acid molecule as disclosed herein.

Another example of the disclosure relates to the anti-Nectin-4 antibodies as defined above, for use in therapy, notably for use in cancer treatment in particular for breast cancer, ovarian cancer or lung cancer treatment. Typically, the cancer is a metastatic cancer.

Another aspect of the present disclosure relates to the anti-Nectin-4 antibody as disclosed herein, for use in therapy.

Another aspect of the present disclosure relates to use of the anti-Nectin-4 antibody as disclosed herein, in the manufacture of a medicament for treating cancer.

The disclosure also encompasses a composition comprising an anti-Nectin-4 antibody according to the present disclosure and at least a pharmaceutically acceptable carrier.

Another aspect of the present disclosure relates to a pharmaceutical composition comprising the anti-Nectin-4 antibody as disclosed herein, and at least a pharmaceutically acceptable carrier.

5 Another example of the disclosure relates to an *in vitro* method for diagnosing cancer in a subject comprising performing an IHC assay on a tissue sample from said subject using an anti-Nectin-4 antibody as herein disclosed, optionally wherein the tissue sample is a fixed tissue sample, notably a fixed embedded tissue sample from said subject, more particularly a Formaldehyde Fixed Paraffin Embedded (FFPE) tissue sample.

10 Another aspect of the present disclosure relates to an *in vitro* method for diagnosing cancer in a subject comprising the detection of the presence or expression level of Nectin-4 in a biological sample wherein the detection is performed by using an anti-Nectin-4 antibody as disclosed herein in an immunohistochemistry (IHC) assay.

15 Another example of the disclosure relates to an *in vitro* method for determining the eligibility of a subject to a treatment with an anti-Nectin-4 antibody as herein described, comprising performing an IHC assay on a tissue sample section from said subject using said anti-Nectin-4 antibody, optionally wherein the tissue sample section is a fixed tissue, notably a fixed embedded tissue sample section from said subject, more particularly a Formaldehyde Fixed Paraffin Embedded (FFPE) tissue section.

20 Another aspect of the present disclosure relates to an *in vitro* method for determining the eligibility of a subject having cancer to a treatment with an anti-Nectin-4 antibody as disclosed herein, wherein the method comprises performing an immunohistochemistry (IHC) assay on a biological sample from said subject using said anti-Nectin-4 antibody.

The disclosure also relates to a method of treating cancer, in a subject in need thereof comprising administering to the subject, a therapeutically effective amount of the anti-Nectin-4 antibody as defined above. In a specific example said method for treating cancer comprises a prior step of

diagnosing cancer or of determining patient eligibility to a treatment with the anti-Nectin-4 antibody, comprising using said anti-Nectin-4 antibody in an IHC assay performed on a tissue sample section from said subject. In particular, the present disclosure encompasses a method of treatment of a patient suffering from or suspected of suffering from a cancer comprising:

- 5 a step 1) of assessing Nectin-4 expression in a tissue sample from a subject suspected of having cancer, or of assessing responsiveness of said cancer patient to an anti-cancer therapeutic agent comprising:

(1a) contacting said tissue sample with the antibody or antigen binding fragment thereof as herein disclosed;

- 10 (1b) detecting the binding of said antibody or antigen binding fragment thereof to said tissue sample; and

(1c) determining the expression of Nectin-4 in the tissue sample, wherein the expression level of Nectin-4 in the tissue sample is compared with a reference expression level of Nectin-4; and

- 15 a step 2) of administering said anti-cancer therapeutic agent to the patient when an increased expression level of Nectin-4 compared to the reference is observed;

optionally wherein, the expression level of Nectin-4 is detected using an immunohistochemistry (IHC) approach, an immunoblotting assay, a fluorescence activated cell sorting (FACS) assay, or an Enzyme-Linked Immunosorbent Assay (ELISA),

- 20 optionally wherein, the anti-cancer therapeutic agent comprises an anti-Nectin-4 antibody or an antibody drug conjugate of an anti-Nectin-4 antibody, typically of an antibody according to the present disclosure or a variant thereof.

Another aspect of the present disclosure relates to use of the anti-Nectin-4 antibody as disclosed herein in the manufacture of a medicament for treating a subject suffering from cancer or suspected
25 of suffering from cancer, wherein the subject is one whose tissue sample had been assessed to have an increased expression level of Nectin-4 following binding of the antibody or antigen binding fragment thereof as disclosed herein with said tissue sample, when compared to a reference expression level of Nectin-4,

- optionally wherein, the expression level of Nectin-4 is detected using an immunohistochemistry
30 (IHC) approach, an immunoblotting assay, a fluorescence activated cell sorting (FACS) assay, or an Enzyme-Linked Immunosorbent Assay (ELISA).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein, the term "Nectin-4" has its general meaning in the art and includes human Nectin-4,
5 in particular the native-sequence polypeptide, isoforms, chimeric polypeptides, all homologs, fragments, and precursors of human Nectin-4. The amino acid sequence for native Nectin-4 includes the NCBI Reference Sequence: **NP_112178.2**.

More specifically the term "Nectin-4" includes the human Nectin-4 of the following SEQ ID:1

10 MPLSLGAEMWGPEAWLLLLLLLLASFTGRCPAGELETSDVVTVVLGQDAKLPCFY
RGDSGEQVGQVAWARVDAGEGAQELALLHSKYGLHVSPAYEGRVEQPPPPRNPL
DGSVLLRNAVQADEGEYECRVSTFPAGSFQARLRRLRVLPPLPSLNPGPALEEGQG

CLAIMS

1. An antibody having specificity for human Nectin-4 and comprising a HCDR1 of SEQ ID NO:2, a HCDR2 of SEQ ID NO:3, a HCDR3 of SEQ ID NO:4, a LCDR1 of SEQ ID NO:5, a LCDR2 of SEQ ID NO:6 and a LCDR3 of SEQ ID NO:7.
- 5 2. The anti-nectin-4 antibody of Claim 1, which competes for binding to Nectin-4 with the reference murine antibody mAb 5A12.2 as obtainable by the hybridoma deposited at the CNCM under deposit number **CNCM I-5407**.
3. The anti-Nectin-4 antibody of claim 1, which comprises:
 - 10 - a variable heavy chain (VH) domain and a variable light chain domain having at least 90 % identity with the heavy chain and light chain of SEQ ID NO:8 and 9 respectively;
or
 - a variable heavy chain (VH) domain and a variable light chain of SEQ ID NO:8 and 9 respectively.
4. The anti-Nectin-4 antibody of claim 1, which is a chimeric or humanized antibody.
- 15 5. The anti-Nectin-4 antibody of any one of claims 1-4, which is characterized in that it has at least one of the following functions:
 - i. it binds to the human Nectin-4 of SEQ ID NO:1 with a K_D of less than 10 $\mu\text{g/mL}$;
 - ii. it selectively binds to Nectin-4 in a biological sample in an immunohistochemistry (IHC) assay.
- 20 6. A nucleic acid molecule, which encodes a heavy chain and a light chain of the anti-Nectin-4 antibody of any one of Claims 1-5.
7. A host cell comprising the nucleic acid molecule of claim 6.
8. The anti-Nectin-4 antibody of any one of claims 1-5, for use in therapy.
9. Use of the anti-Nectin-4 antibody of any one of claims 1-5, in the manufacture of a medicament
25 for treating cancer.
10. The use according to claim 9, wherein the cancer is selected from breast cancer, ovarian cancer, bladder, urothelial, pancreatic or lung cancer treatment.
11. The use according to claim 9 or 10, wherein the cancer is metastatic cancer.
12. A pharmaceutical composition comprising the anti-Nectin-4 antibody of any one of Claims 1-5,
30 and at least a pharmaceutically acceptable carrier.

13. An *in vitro* method for diagnosing cancer in a subject comprising the detection of the presence or expression level of Nectin-4 in a biological sample wherein the detection is performed by using an anti-Nectin-4 antibody according to any one of claims 1 to 5 in an immunohistochemistry (IHC) assay.
- 5 14. An *in vitro* method for determining the eligibility of a subject having cancer to a treatment with an anti-Nectin-4 antibody according to any one of claims 1 to 5, wherein the method comprises performing an immunohistochemistry (IHC) assay on a biological sample from said subject using said anti-Nectin-4 antibody.
- 10 15. The *in vitro* method of claim 13 or 14, wherein the biological sample section is a fixed tissue, optionally a formalin-fixed paraffin-embedded (FFPE) tissue.
- 15 16. Use of the anti-Nectin-4 antibody according to any one of claims 1 to 5 in the manufacture of a medicament for treating a subject suffering from cancer or suspected of suffering from cancer, wherein the subject is one whose tissue sample had been assessed to have an increased expression level of Nectin-4 following binding of the antibody or antigen binding fragment thereof of any one of claims 1-5 with said tissue sample, when compared to a reference expression level of Nectin-4,
- optionally wherein, the expression level of Nectin-4 is detected using an immunohistochemistry (IHC) approach, an immunoblotting assay, a fluorescence activated cell sorting (FACS) assay, or an Enzyme-Linked Immunosorbent Assay (ELISA).