

**CLAIMS**

1. An immunoconjugate comprising an antibody which:
  - a) binds to the domain consisting of the first to third loops of human LAMP1 protein which consists of amino acids Ala29 to Ile309 of SEQ ID NO: 24, and
  - b) is linked or conjugated to at least one growth inhibitory agent.
2. The immunoconjugate according to claim 1, wherein the antibody binds to a first luminal domain of human LAMP1 protein; wherein the first luminal domain of human LAMP1 protein consists of amino acids at positions Ala29 to Arg195 of SEQ ID NO: 24.
3. The immunoconjugate according to any one of claims 1 or 2, wherein the antibody competes for binding to the first luminal domain of human LAMP1 proteins with an antibody comprising the variable heavy and light chains of
  - (i) an antibody comprising a variable domain of heavy chain of sequence SEQ ID NO: 1 and a variable domain of light chain of sequence SEQ ID NO: 5; or
  - (ii) an antibody comprising a variable domain of heavy chain of sequence SEQ ID NO: 8 and a variable domain of light chain of sequence SEQ ID NO: 12; or
  - (iii) an antibody comprising a variable domain of heavy chain of sequence SEQ ID NO: 15 and a variable domain of light chain of sequence SEQ ID NO: 16; or
  - (i) an antibody comprising a variable domain of heavy chain of sequence SEQ ID NO: 42 and a variable domain of light chain of sequence SEQ ID NO: 46; or
  - (iv) an antibody comprising a variable domain of heavy chain of sequence SEQ ID NO: 42 and a variable domain of light chain of sequence SEQ ID NO: 51; or
  - (v) an antibody comprising a variable domain of heavy chain of sequence SEQ ID NO: 53 and a variable domain of light chain of sequence SEQ ID NO: 56; or
  - (vi) an antibody comprising a variable domain of heavy chain of sequence SEQ ID NO: 54 and a variable domain of light chain of sequence SEQ ID NO: 57; or
  - (vii) an antibody comprising a variable domain of heavy chain of sequence SEQ ID NO: 55 and a variable domain of light chain of sequence SEQ ID NO: 58.

4. The immunoconjugate according to any one of claims 1 to 3 wherein the antibody comprises:

- (i) a CDR1-H of sequence SEQ ID NO: 2, a CDR2-H of sequence SEQ ID NO: 3, and a CDR3-H of sequence SEQ ID NO: 4 ; and  
a CDR1-L of sequence SEQ ID NO: 6, a CDR2-L of sequence DTS and a CDR3-L of sequence SEQ ID NO: 7; or
- (ii) a CDR1-H of sequence SEQ ID NO: 9 , a CDR2-H of sequence SEQ ID NO: 10, a CDR3-H of sequence SEQ ID NO: 11; and  
a CDR1-L of sequence SEQ ID NO: 13, a CDR2-L of sequence AAS, and a CDR3-L of sequence SEQ ID NO: 14; or
- (iii) a CDR1-H of sequence SEQ ID NO: 43 , a CDR2-H of sequence SEQ ID NO: 44, and a CDR3-H of sequence SEQ ID NO: 45; and  
a CDR1-L of sequence SEQ ID NO: 47, a CDR2-L of sequence YTS, and a CDR3-L of sequence SEQ ID NO: 48 or SEQ ID NO: 52 .

5. The immunoconjugate according to any one of claims 1 to 4, wherein the antibody comprises:

- (i) a CDR1-H of sequence SEQ ID NO: 2, a CDR2-H of sequence SEQ ID NO: 3, a CDR3-H of sequence SEQ ID NO: 4, a CDR1-L of sequence SEQ ID NO: 6, a CDR2-L of sequence DTS, and a CDR3-L of sequence SEQ ID NO: 7; or
- (ii) a CDR1-H of sequence SEQ ID NO: 9, a CDR2-H of sequence SEQ ID NO: 10, a CDR3-H of sequence SEQ ID NO: 11, a CDR1-L of sequence SEQ ID NO: 13, a CDR2-L of sequence AAS, and a CDR3-L of sequence SEQ ID NO: 14; or
- (iii) a CDR1-H of sequence SEQ ID NO: 43, a CDR2-H of sequence SEQ ID NO: 44, a CDR3-H of sequence SEQ ID NO: 45, a CDR1-L of sequence SEQ ID NO: 47, a CDR2-L of sequence YTS, and a CDR3-L of sequence SEQ ID NO: 48 or SEQ ID NO: 52;

6. The immunoconjugate according to any one of claims 1 to 5, wherein the antibody comprises:

- (i) a variable domain of heavy chain of sequence SEQ ID NO: 1 and a variable domain of light chain of sequence SEQ ID NO: 5; or
- (ii) a variable domain of heavy chain of sequence SEQ ID NO: 8, and a variable domain of light chain of sequence SEQ ID NO: 12; or
- (iii) a variable domain of heavy chain of sequence SEQ ID NO: 15, and a

- variable domain of light chain of sequence SEQ ID NO: 16; or
- (iv) a variable domain of heavy chain of sequence SEQ ID NO: 42, and a variable domain of light chain of sequence SEQ ID NO: 46 or SEQ ID NO: 51, or
  - (v) a variable domain of heavy chain of sequence SEQ ID NO: 53 and a variable domain of light chain of sequence SEQ ID NO: 56; or
  - (vi) a variable domain of heavy chain of sequence SEQ ID NO: 54 and a variable domain of light chain of sequence SEQ ID NO: 57; or
  - (vii) a variable domain of heavy chain of sequence SEQ ID NO: 55 and a variable domain of light chain of sequence SEQ ID NO: 58.
7. The immunoconjugate according to any one of claims 1 to 6, wherein the antibody does not significantly cross-react with human LAMP2 (SEQ ID NO: 40).
8. The immunoconjugate according to any one of claims 1 to 7, wherein the antibody has an apparent affinity measured via flow cytometry for human LAMP 1 expressed on the cell surface of a recombinant cell line, which is  $\leq 35\text{nM}$ .
9. The immunoconjugate according to any one of claims 1 to 8 wherein the antibody is a chimeric or a humanised antibody.
10. The immunoconjugate according to any one of claims 1 to 9, wherein the antibody comprises:
- i) a heavy chain of sequence SEQ ID NO: 17 and a light chain of sequence SEQ ID NO: 18; or
  - ii) a heavy chain of sequence SEQ ID NO: 19 and a light chain of sequence SEQ ID NO: 20; or
  - iii) a heavy chain of sequence SEQ ID NO: 21 and a light chain of sequence SEQ ID NO: 22; or
  - iv) a heavy chain of sequence SEQ ID NO: 49 and a light chain of sequence SEQ ID NO: 50; or
  - v) a heavy chain of sequence SEQ ID NO: 49 and a light chain of sequence SEQ ID NO: 81; or
  - vi) a heavy chain of sequence SEQ ID NO: 60 and a light chain of sequence SEQ ID NO: 59; or
  - vii) a heavy chain of sequence SEQ ID NO: 62 and a light chain of sequence SEQ ID NO: 61; or

viii) a heavy chain of sequence SEQ ID NO: 64 and a light chain of sequence SEQ ID NO: 63.

11. The immunoconjugate according to any one of claims 1 to 10, wherein the antibody is a bispecific antibody.

12. The immunoconjugate according to any one of claims 1 to 10, wherein the antibody is a multispecific antibody.

13. The immunoconjugate according to any one of claims 1 to 12, wherein said at least one growth inhibitory agent is a cytotoxic agent or a radioactive isotope.

14. The immunoconjugate according to any one of claims 1 to 13, wherein said at least one growth inhibitory agent is selected from the group consisting of chemotherapeutic agents, enzymes, antibiotics, toxins, taxoids, vincas, taxanes, maytansinoid or maytansinoid analogs, tomaymycin or pyrrolobenzodiazepine derivatives, cryptophycin derivatives, leptomycin derivatives, auristatin or dolastatin analogs, prodrugs, topoisomerase II inhibitors, DNA alkylating agents, anti-tubulin agents, and CC-1065 or CC-1065 analogs.

15. The immunoconjugate according to any one of claims 1 to 14, wherein said at least one growth inhibitory agent is selected from the group consisting of At<sup>211</sup>, Ac<sup>225</sup>, Bi<sup>212</sup>, Er<sup>169</sup>, I<sup>131</sup>, I<sup>124</sup>, I<sup>125</sup>, Y<sup>90</sup>, In<sup>111</sup>, P<sup>32</sup>, Re<sup>186</sup>, Re<sup>188</sup>, Sm<sup>153</sup>, Sr<sup>89</sup>, Zr<sup>89</sup>, Tc<sup>99m</sup>, Ga<sup>68</sup>, Cu<sup>64</sup>, radioactive isotopes of Lu, and Th<sup>227</sup>.

16. The immunoconjugate according to any one of claims 1 to 15, wherein said at least one growth inhibitory agent is

(i) a cytotoxic agent selected from the group consisting of enzymes other than from pokeweed antiviral protein; antibiotics other than from bleomycin and mitomycin; toxins of bacterial, fungal, or animal origin or of plant origin other than from abrin and ricin, including fragments and/or variants thereof; a drug or a pro-drug of a compound consisting in an anti-tubulin agent, a maytansinoid or maytansinoid analog, a taxoid or taxane other than from paclitaxel (Taxol), a vinca-alkaloid other than from vindesine, vincristine and vinblastine, a cryptophycin derivative, an auristatin or dolastatin analog; a DNA alkylating agent other than from BCNU and cyclophosphamide; a tomaymycin or pyrrolobenzodiazepine derivative, a CC-1065 or CC-1065 analog; a leptomycin derivative; a topoisomerase II inhibitors other than doxorubicin (adriamycin) and etoposide, a RNA polymerase II inhibitor, alpha-amanitin or

(ii) a radioactive isotopes selected from the group consisting of At<sup>211</sup>, Ac<sup>225</sup>, Bi<sup>213</sup>, Pb<sup>212</sup>, Er<sup>169</sup>, I<sup>124</sup>, I<sup>125</sup>, In<sup>111</sup>, P<sup>32</sup>, Re<sup>186</sup>, Sm<sup>153</sup>, Sr<sup>89</sup>, Zr<sup>89</sup>, Tc<sup>99m</sup>, Ga<sup>68</sup>, Cu<sup>64</sup> and radioactive isotopes of Lu such as Lu<sup>177</sup>, and Th<sup>227</sup>.

17. The immunoconjugate according to any one of claims 1 to 13, wherein said growth inhibitory agent is (*N*<sup>2</sup>-deacetyl-*N*<sup>2'</sup>-(3-mercapto-1-oxopropyl)-maytansine) (DM1) or *N*<sup>2</sup>-deacetyl-*N*<sup>2'</sup>-(4-methyl-4-mercapto-1-oxopentyl)-maytansine (DM4).

18. The immunoconjugate according to any one of the claims 1 to 17, wherein the antibody is covalently attached via a cleavable or non-cleavable linker to the at least one growth inhibitory agent.

19. The immunoconjugate according to claim 18, wherein said linker is selected from the group consisting of N-succinimidyl pyridyldithiobutyrate (SPDB), 4-(Pyridin-2-ylidisulfanyl)-2-sulfo-butyric acid (sulfo-SPDB), and succinimidyl (N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC).

20. The immunoconjugate according to claim 18, wherein said linker is N-succinimidyl pyridyldithiobutyrate (SPDB) and the growth inhibitory agent is *N*<sup>2</sup>-deacetyl-*N*<sup>2'</sup>-(4-methyl-4-mercapto-1-oxopentyl)-maytansine (DM4).

21. The immunoconjugate according to claim 18, wherein said linker is 4-(Pyridin-2-ylidisulfanyl)-2-sulfo-butyric acid (sulfo-SPDB) and the growth inhibitory agent is *N*<sup>2</sup>-deacetyl-*N*<sup>2'</sup>-(4-methyl-4-mercapto-1-oxopentyl)-maytansine (DM4).

22. The immunoconjugate according to claim 18, wherein said linker is succinimidyl (N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and the growth inhibitory agent is *N*<sup>2</sup>-deacetyl-*N*<sup>2'</sup>-(3-mercapto-1-oxopropyl)-maytansine (DM1).

23. The immunoconjugate according to any one of claims 1 to 22, wherein the immunoconjugate is characterised by a drug-to-antibody ratio (DAR) ranging from 1 to 10, preferably between 2 to 5, more preferably between 3 to 4, the DAR being calculated from the ratio of the drug concentration to that of the antibody :

$$\text{DAR} = c_D / c_A$$

wherein

$$c_D = [(\epsilon_{A280} \times A_{252}) - (\epsilon_{A252} \times A_{280})] / [(\epsilon_{D252} \times \epsilon_{A280}) - (\epsilon_{A252} \times \epsilon_{D280})]$$

$$c_A = [A_{280} - (c_D \times \epsilon_{D280})] / \epsilon_{A280}$$

and

$\epsilon_{D252}$  and  $\epsilon_{D280}$  are respectively the molar extinction coefficients of the drug at 252 nm and 280 nm;

$\epsilon_{A252}$  and  $\epsilon_{A280}$  are respectively the molar extinction coefficients of the antibody at 252 nm and 280 nm;

( $A_{252}$ ) and  $A_{280}$  are respectively the absorbances for the conjugate at 252 nm ( $A_{252}$ ) and at 280 nm ( $A_{280}$ ), measured using a classic spectrophotometer apparatus.

24. The immunoconjugate according to any one of claims 1 to 23, wherein at least 2 molecules of antibody according to the invention are internalized by one molecule of LAMP1 expressed at the surface of a cancer cell.

25. An immunoconjugate comprising an antibody which binds to human LAMP1 protein linked or conjugated to at least one growth inhibitory agent, wherein the antibody comprises:

- (i) a CDR1-H of sequence SEQ ID NO: 2, a CDR2-H of sequence SEQ ID NO: 3, a CDR3-H of sequence SEQ ID NO: 4, a CDR1-L of sequence SEQ ID NO: 6, a CDR2-L of sequence DTS, and a CDR3-L of sequence SEQ ID NO: 7.

26. An immunoconjugate comprising an antibody linked or conjugated to at least one growth inhibitory agent, wherein the antibody comprises:

- (i) a variable domain of heavy chain of sequence SEQ ID NO: 1 and a variable domain of light chain of sequence SEQ ID NO: 5; or
- (ii) a variable domain of heavy chain of sequence SEQ ID NO: 53 and a variable domain of light chain of sequence SEQ ID NO: 56; or
- (iii) a variable domain of heavy chain of sequence SEQ ID NO: 54 and a variable domain of light chain of sequence SEQ ID NO: 57; or
- (iv) a variable domain of heavy chain of sequence SEQ ID NO: 55 and a variable domain of light chain of sequence SEQ ID NO: 58.
- (v) or a fragment of an antibody as defined in (i) to (iv).

27. The isolated antibody which comprises

- (i) a CDR1-H of sequence SEQ ID NO: 2, a CDR2-H of sequence SEQ ID NO: 3, and a CDR3-H of sequence SEQ ID NO: 4; and a CDR1-L of sequence SEQ ID NO: 6, a CDR2-L of sequence DTS, and a CDR3-L of sequence SEQ ID NO: 7; or
- (ii) a CDR1-H of sequence SEQ ID NO: 9, a CDR2-H of sequence SEQ ID NO: 10, a CDR3-H of sequence SEQ ID NO: 11; and

- a CDR1-L of sequence SEQ ID NO: 13, a CDR2-L of sequence AAS, and a CDR3-L of sequence SEQ ID NO: 14; or
- (iii) a CDR1-H of sequence SEQ ID NO: 43, a CDR2-H of sequence SEQ ID NO: 44, and a CDR3-H of sequence SEQ ID NO: 45, and  
a CDR1-L of sequence SEQ ID NO: 47, a CDR2-L of sequence YTS, and a CDR3-L of sequence SEQ ID NO: 48 or SEQ ID NO: 52.
28. A pharmaceutical composition comprising an immunoconjugate according to any one of claims 1 to 26, or an antibody according to claim 27, and a pharmaceutically acceptable carrier.
29. An antibody according to claim 27 for use for *ex vivo* detecting LAMP1 expression in biological sample of a subject.
30. An antibody according to claim 27 for use for *in vivo* detecting LAMP1 expression in a subject.
31. The antibody for the use according to claim 29 or 30, wherein said antibody is labelled with a detectable molecule or substance.
32. The antibody for the use according to any one of claims 29 or 30, wherein said use is for diagnosing the presence of a cancer in a subject, determining susceptibility of a patient having cancer to a therapeutic agent targeting LAMP1, or monitoring effectiveness of anti-LAMP1 cancer therapy or detecting cancer relapse after anti-LAMP1 cancer therapy.
33. An isolated nucleic acid comprising a sequence encoding an antibody according to claim 27.
34. A host cell which has been transformed by a nucleic acid according to claim 33.
35. Use of an effective amount of an immunoconjugate according to any one of claims 1 to 26, or an antibody according to claim 27, or a pharmaceutical composition according to claim 28 for the manufacture of a medicament for treating a cancer.
36. The use according to claim 35, wherein the cancer is colon cancer adenocarcinoma, gastrointestinal tumors, vital organs tumors, reproductive organ tumors, or skin, larynx or soft tissue tumor.

37. The use according to claim 35, wherein said use comprises selecting patients with cancer who are likely to respond to anti-LAMP1 therapy by determining, in a biological sample of a patient with cancer which includes cancer cells, if said patient harbors a LAMP1 gene copy number gain.

38. The use according to claim 37, which further comprises determining if LAMP1 is expressed at the surface of cancer cells of the patient.

39. The use according to any one of claims 37 and 38, wherein LAMP1 gene copy number gain is determined with a method selected from the group consisting of Fluorescence In Situ Hybridization (FISH), Comparative Genomic Hybridization (CGH), New Generation Sequencing (NGS) or Polymerase Chain Reaction (PCR).