

Claims

1. An antibody or antigen-binding fragment thereof with binding specificity for integrin alpha10, wherein the antibody or antigen-binding fragment comprises:
 - a light chain variable region comprising
 - a) a CDR-L1 comprising an amino acid sequence of SEQ ID NO: 1;
 - b) a CDR-L2 comprising an amino acid sequence of SEQ ID NO: 2; and
 - c) a CDR-L3 comprising an amino acid sequence of SEQ ID NO: 3;
 and
 - a heavy chain variable region comprising
 - d) a CDR-H1 comprising an amino acid sequence selected from SEQ ID NO: 4, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:7;
 - e) a CDR-H2 comprising an amino acid sequence of SEQ ID NO: 8; and
 - f) a CDR-H3 comprising an amino acid sequence of SEQ ID NO: 9,
 and
 - wherein the antibody or antigen-binding fragment thereof binds to the extracellular I-domain of the integrin alpha10 subunit.
2. The antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment comprises:
 - a) an immunoglobulin light chain variable region comprising or consisting of the amino acid sequence selected from SEQ ID NO: 10, SEQ ID NO:11 and SEQ ID NO:12 or a sequence having at least 85% sequence identity to any of SEQ ID NO: 10, SEQ ID NO:11 and SEQ ID NO:12, such as at least 95%, such as 98% or 99% sequence identity to any of SEQ ID NO: 10, SEQ ID NO:11 and SEQ ID NO:12; and/or
 - b) an immunoglobulin heavy chain variable region comprising or consisting of the amino acid sequence selected from SEQ ID NO: 13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18 and SEQ ID NO:19 or a sequence having at least 85% sequence identity to any of SEQ ID NO: 13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18 and SEQ ID NO:19, such as at least 95%, such as 98% or 99% sequence identity to any of SEQ ID NO: 13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18 and SEQ ID NO:19.
3. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment comprises:

- a) an immunoglobulin light chain variable region comprising CDR-L1 of SEQ ID NO:1, CDR-L2 of SEQ ID NO:2 and CDR-L3 of SEQ ID NO:3; and
 - b) an immunoglobulin heavy chain variable region comprising
 - i. CDR-H1 of SEQ ID NO:4, CDR-H2 of SEQ ID NO:8 and CDR-H3 of SEQ ID NO:9, or
 - ii. CDR-H1 of SEQ ID NO:5, CDR-H2 of SEQ ID NO:8 and CDR-H3 of SEQ ID NO:9.

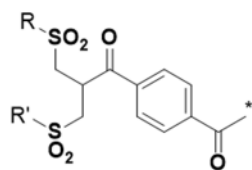
- 4. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment comprises:
 - a) an immunoglobulin light chain variable region comprising or consisting of the amino acid sequence of SEQ ID NO: 12; and
 - b) an immunoglobulin heavy chain variable region comprising or consisting of the amino acid sequence of SEQ ID NO: 16.

- 5. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment comprises: a light chain variable region comprising
 - a) a CDR-L1 comprising or consisting of an amino acid sequence of SEQ ID NO: 1;
 - b) a CDR-L2 comprising or consisting of an amino acid sequence of SEQ ID NO: 2; and
 - c) a CDR-L3 comprising or consisting of an amino acid sequence of SEQ ID NO: 3;
 and a heavy chain variable region comprising
 - d) a CDR-H1 comprising or consisting of an amino acid sequence of SEQ ID NO: 4;
 - e) a CDR-H2 comprising or consisting of an amino acid sequence of SEQ ID NO: 8; and
 - f) a CDR-H3 comprising or consisting of an amino acid sequence of SEQ ID NO: 9.

6. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, comprising or consisting of an antigen-binding fragment selected from: a Fab fragment, a Fab' fragment, an F(ab')₂ fragment, an Fv, a single chain antibody (SCA) such as an scFv, a disulphide-bonded Fv, the variable portion of the heavy and/or light chains thereof, and a Fab miniantibody, and wherein the antibody or antigen-binding fragment thereof comprises an Fc region and/or an intact antibody.
7. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is conjugated to an additional moiety, such as a toxin, a chemotherapeutic agent and a radioactive tracer, or combinations thereof.
8. A polynucleotide, such as a cDNA molecule, encoding an antibody or antigen-binding fragment thereof according to any one of the preceding claims or a component polypeptide chain thereof.
9. A method for producing an antibody or antigen-binding fragment thereof according to any one of claims 1 to 7, the method comprising culturing a host cell comprising the polynucleotide according to claim 8, under conditions which permit expression of the encoded antibody or antigen-binding fragment thereof.
10. An *in vitro* method for the detection of cells expressing integrin alpha10beta1 in a subject, the method comprising:
 - a) providing a sample of cells from a subject to be tested, such as biopsy tissue or blood sample;
 - b) optionally, extracting and/or purifying the cells present in the sample;
 - c) contacting an antibody or antigen-binding fragment thereof according to any one of claims 1 to 7 with cells present in the sample;
 - d) determining whether the antibody or antigen-binding fragment thereof binds to the cells
 wherein the binding of the antibody or antigen-binding fragment thereof to the cells is indicative of the presence of a disease or disorder associated with cells expression integrin alpha10 in the tissue of a subject.

11. A method for *in vivo* imaging the expression of the integrin alpha10beta1 in a mammal, the method comprising the steps of
- a) providing a mammal,
 - b) providing an antibody or antigen-binding fragment thereof according to any one of claims 1 to 7,
 - c) administering the antibody or antigen-binding fragment thereof according to any one of claims 1 to 7 to the mammal so as to allow the antibody or a fragment thereof to bind to an extracellular domain of integrin alpha10beta1 of cells in said mammal,
 - d) optionally adding a second labelled antibody or a fragment thereof to the sample, wherein the second antibody or a fragment thereof binds to the antibody or a fragment thereof in c),
 - e) detecting the antibody or antigen-binding fragment thereof according to any one of claims 1 to 7 of said cells in c), or optionally detecting the second labelled antibody or a fragment thereof in d) bound to the antibody or a fragment thereof, and
 - f) creating an image of the detected antibody or a fragment thereof, thereby imaging the expression of integrin alpha10beta1 on cells in a mammal *in vivo*.
12. An antibody-drug conjugate directed against integrin alpha10 comprising:
- a) an antibody or antigen-binding fragment thereof according to any one of the preceding claims 1 to 7,
 - b) an active agent, and
 - c) optionally, a linker which links a) to b).
13. The antibody-drug conjugate according to claim 12, wherein the active agent is a therapeutic agent selected from: microtubule toxins, immunomodulators, nucleotide based agents, DNA toxins and transcription toxins or, a cytotoxic agent, or a microtubule toxin selected from the group consisting of Auristatin-based toxins, Maytansinoid-based toxins, Tubulysins-based toxins and Eribulin or a transcription toxin such as an RNA polymerase II and/or III inhibiting agent.

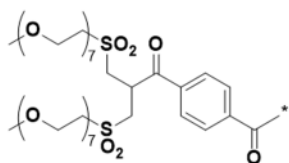
14. The antibody-drug conjugate according to claim 12, wherein the active agent is a transcription toxin selected from Doxorubicin, Doxorubicin derivatives, such as 3'-deamino-3''-4'-anhydro-[2''(S)-methoxy-3''(R)-hydroxy-4''-morpholinyl]doxorubicin (PNU159682), and Amanitin.
15. The antibody-drug conjugate according to any one of claims 12 and 14, wherein the active agent is 3'-deamino-3''-4'-anhydro-[2''(S)-methoxy-3''(R)-hydroxy-4''-morpholinyl]doxorubicin (PNU159682).
16. The antibody-drug conjugate according to any one of claims 12 to 15, wherein the antibody-drug conjugate comprises a conjugating unit, such as a conjugating unit derived from a reactive group such as a functionalized benzoic acid, an activated carboxylic acid derivative, an amino group, a maleimide group or derivatives thereof, N-hydroxysuccinimide, bis-sulfones, azides and alkynes.
17. The antibody-drug conjugate according to any one of claims 12 to 16, wherein the conjugating unit is;
- a) derived from a functionalized bis-sulfone group, such as a bis-sulfone group according to Formula C



Formula C,

wherein * indicates an attachment site to a linker, and wherein R and R' are each independently selected from the group consisting of selected from the group consisting of C₁-C₆ alkyl, a C₃-C₇ cycloalkyl, a C₃-C₇ heterocycloalkyl, phenyl, C₅-C₁₀ aryl, each of which may optionally be substituted by one or more selected from halogen, cyano, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, and C₅-C₁₀ aryl, or

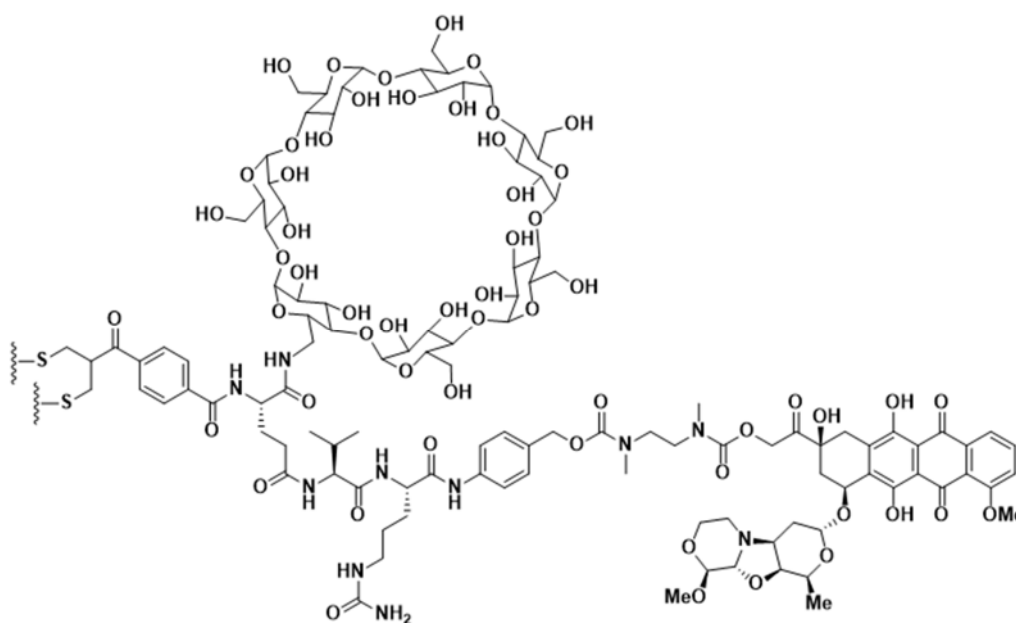
b) derived from a functionalized bis-sulfone group according to Formula C'' (bis-mPEG):



Formula C'', wherein * indicates an attachment site to a linker.

18. The antibody-drug conjugate according to any one of claims 12 to 17, wherein the antibody-drug conjugate comprises:

bis-mPEG-Glu-(Val-cit-PAB-DMEDA-PNU159682)-6'-amino- β -cyclodextrin, as in Formula A



Formula A, wherein  indicates the attachment to an antibody or antigen-binding fragment thereof.

19. The antibody-drug conjugate according to any one of claims 12 to 18, wherein the antibody-drug conjugate comprises:

- a) the antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment thereof comprises
 - a light chain variable region comprising a CDR-L1 consisting of SEQ ID NO:1, a CDR-L2 consisting of SEQ ID NO:2 and a CDR-L3 consisting of SEQ ID NO:3; and

- a heavy chain variable region comprising a CDR-H1 consisting of any one of SEQ ID NO: 4, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:7, a CDR-H2 consisting of SEQ ID NO:8 and a CDR-H3 consisting of SEQ ID NO:9; and
 - b) a conjugating unit, such as a conjugating unit derived from a bis-sulfone group according to formula C'' and functionalized with a glutamic acid (bis-mPEG-Glu);
 - c) a linker comprising or consisting of Val-cit-PAB-DMEDA;
 - d) a functional unit, such as 6'-amino- β -cyclodextrin; and
 - e) the active agent PNU159682.
20. Use of the antibody-drug conjugate according to any one claims 12 to 19 for the manufacture of a medicament.
21. Use of the antibody-drug conjugate according to any one claims 12 to 19 for the manufacture of a medicament for the treatment of a disease or disorder associated with cells expressing integrin $\alpha 10$.
22. Use of the antibody-drug conjugate according to any one claims 12 to 19 for the manufacture of a medicament for the treatment of a neoplastic disease or disorder, such as wherein the neoplastic disease or disorder is a solid tumour, a lymphoma or a cancer, wherein the cancer is selected from the group consisting of breast cancer, brain cancer, cancer of the Central Nervous System (CNS), lung cancer, prostate cancer, pancreatic cancer, skin cancer, lymphoma, sarcoma, rhabdoid tumor, cholangiocarcinoma, or a metastasis of any one of said cancer forms.