CLAIMS

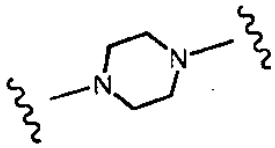
1. An antibody-drug conjugate having the general formula A – $(L\text{-}T)_n$, wherein
   a. A is an antibody or fragment thereof binding to CLDN18.2 comprising the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO: 23 respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 24, SEQ ID NO: 25 and SEQ ID NO: 26 respectively,
   b. L is a linker, and
   c. T is a toxin,
      wherein the toxin is an anthracycline,

   wherein n is an integer between ≥1 and ≤ 10;

   or a pharmaceutically acceptable salt or ester thereof.

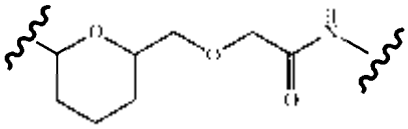
2. The antibody-drug conjugate of claim 1, wherein the linker L comprises at least one a non-cleavable linker element, preferably wherein the non-cleavable linker element is selected from the group consisting of

   a. ethylenediamine (EDA),
   b. N-formyl-N,N'-dimethylethylenediamine,
   c. diethylamine (DEA),
   d. a piperazine-derived compound of the following formula:



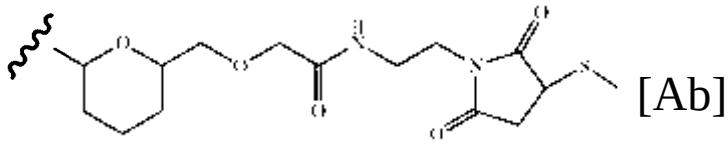
   wherein the wavy lines indicate attachments to the toxin and another linker element,

   e. the compound of the following formula:



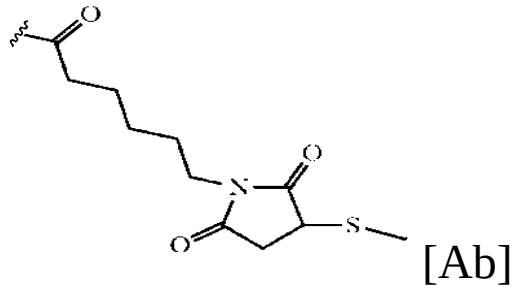
   wherein the wavy lines indicate attachments to the toxin and another linker element,

   f. the compound of the following formula:



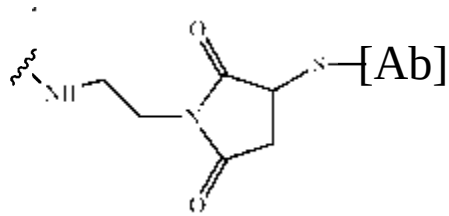
wherein the wavy lines indicate attachments to the toxin and [Ab] indicates the antibody or fragment thereof,

g. a maleimidocaproyl compound of the following formula:



wherein the wavy lines indicate attachments to another linker element and [Ab] indicates the antibody or fragment thereof,

h. the compound of the following formula:



wherein the wavy lines indicate attachments to a toxin and [Ab] indicates the antibody or fragment thereof,

and wherein the non-cleavable linker element is conjugated to the toxin by means of an amide bond or an ether bond.

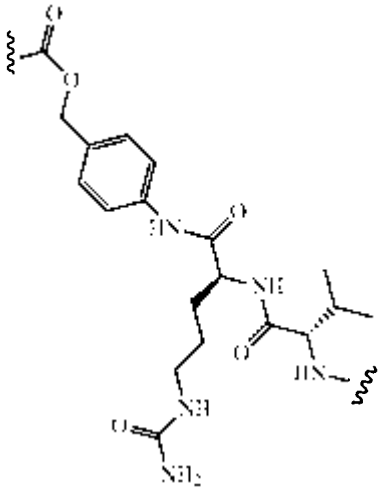
3. The antibody-drug conjugate of claim 2, wherein the linker further comprises an oligopeptide linker element and/or enzyme-cleavable linker element and/or a spacer element.

4. The antibody-drug conjugate of claim 3, wherein one oligopeptide linker element comprises a sortase recognition motif oligopeptide selected from: - LPXTG$_m$-, -LPXAG$_m$-, -LPXSG$_m$-, -LAXTG$_m$-, -LPXTG$_m$-, -LPXTA$_m$-, -NPQTG$_m$- or -NPQTN$_m$-, with G$_m$ being an oligoglycine with m being an integer between ≥1 and ≤ 21, A$_m$ being an oligoalanine with m being an integer between ≥ 1 and ≤ 21, N$_m$ being an oligoasparagine with m being an integer between ≥ 1 and ≤ 21 and X being any

conceivable amino acid, preferably the sortase recognition motif oligopeptide being -LPQTGG- or -LPETGG-, preferably wherein the oligopeptide linker element comprises:

a. the sequence SEQ ID NO: 131, or
b. the sequence SEQ ID NO: 132.

5. The antibody-drug conjugate of any of claim 3 or claim 4, wherein the enzyme-cleavable linker element comprises a val-cit-PAB linker according to the compound of the following formula:



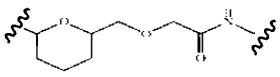
wherein the wavy lines indicate attachments to other linker elements.

6. The antibody-drug conjugate of any of claims 3 to 5, wherein the spacer element comprises a peptidic flexible oligopeptide, preferably wherein the peptidic flexible oligopeptide consists of G and S, more preferably wherein the peptidic flexible oligopeptide is $(GGGGS)_o$ with o being 1, 2, 3, 4 or 5.

7. The antibody-drug conjugate of any of claims 1 to 6, wherein the antibody drug conjugate has the following structure:

a. A – ([oligopeptide linker element – non-cleavable linker element] – $T)_n$ and preferably wherein the linker is selected from:

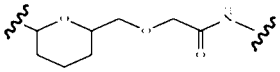
i. [LPXTGG]-[ethylenediamine], and

ii. [LPXTGG]-[];

b. A – ([oligopeptide linker element – enzyme cleavable linker element – non-cleavable linker element] – T) $_n$ and preferably wherein the linker is selected from:

   i. [LPXTGG]-[vc-PAB]-[N-formyl-N,N'-dimethylethylenediamine], and
   ii. [LPXTGG]-[vc-PAB]-[piperazine];

c. A – ([spacer element – oligopeptide linker element – non-cleavable linker element] – T) $_n$ and preferably wherein the linker is selected from:

   i. [GGGGS]-[LPXTGG]-[ethylenediamine], and
   ii. [GGGGS]-[LPXTGG]-[]; or

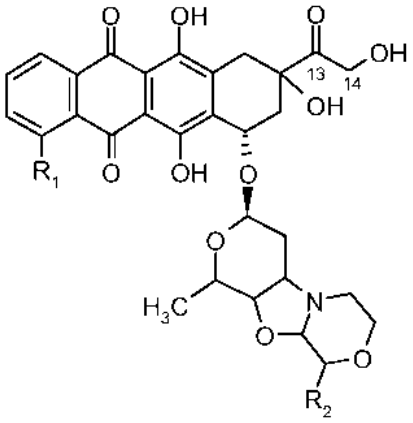
d. A – ([spacer element – oligopeptide linker element – enzyme cleavable linker element – non-cleavable element] – T) $_n$ and preferably wherein the linker is selected from:

   i. [GGGGS]-[LPXTGG]-[vc-PAB]-[N-formyl-N,N'-dimethylethylenediamine], and
   ii. [GGGGS]-[LPXTGG]-[vc-PAB]-[piperazine].

8. The antibody-drug conjugate of claim 7, wherein the non-cleavable linker element is ethylenediamine and wherein the oligopeptide linker element is LPXTGG wherein X is Q or E, preferably wherein X is Q.

9. The antibody-drug conjugate of any of claims 1 to 8, wherein
   a. (L-T) is covalently linked to both light chains of the antibody,
   b. (L-T) is covalently linked to both heavy chains of the antibody, or
   c. (L-T) is covalently linked to both light chains and both heavy chains of the antibody.

10. The antibody-drug conjugate of any of claims 1 to 9, wherein the anthracycline derivative has the following formula (I), and is covalently linked to the non-cleavable linker element by the C_{13} resulting in the loss of the C_{14} and the hydroxyl group, or is covalently linked to the non-cleavable linker element by the hydroxyl group on C_{14}:



(I)

and wherein R_1 is a hydrogen atom, a hydroxy or methoxy group,
and wherein R_2 is a C_1-C_5 alkoxy group, preferably wherein the anthracycline derivative is a derivative of 3'-deamino-3'',4'-anhydro-[2''(S)-methoxy-3''(R)-oxy-4''-morpholinyl]doxorubicin (PNU-159682).

11. The antibody-drug conjugate of any of claims 1 to 10, wherein A, the antibody or fragment thereof, comprises:

    a. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 15 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;

    b. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 16 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;

    c. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 16 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 17, SEQ ID NO: 14 and SEQ ID NO: 11, respectively;

    d. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 16 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 11, respectively;

    e. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID NO: 15 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;

f. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 20 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;

g. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 20 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 11, respectively;

h. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID NO: 20 and SEQ ID NO: 8, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively; or

i. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID NO: 20 and SEQ ID NO: 8, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 17, SEQ ID NO: 14 and SEQ ID NO: 11, respectively.

12. The antibody-drug conjugate of any of claims 1 to 10, wherein A, the antibody or fragment thereof comprises:

a. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;

b. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 7 and SEQ ID NO: 8, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 9, SEQ ID NO: 10 and SEQ ID NO: 11, respectively; or

c. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID NO: 2 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 13, SEQ ID NO: 14 and SEQ ID NO: 11, respectively,

preferably wherein A, the antibody or fragment thereof comprises:

a. a VH sequence of SEQ ID NO: 27 and a VL sequence of SEQ ID NO: 28;

b. a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 30; or

a VH sequence of SEQ ID NO: 31 and a VL sequence of SEQ ID NO: 32.

13. The antibody-drug conjugate of any of claims 1 to 11, wherein A, the antibody or fragment thereof comprises:

a. a VH sequence of SEQ ID NO: 33 and a VL sequence of SEQ ID NO: 38;

b. a VH sequence of SEQ ID NO: 34 and a VL sequence of SEQ ID NO: 38;

c. a VH sequence of SEQ ID NO: 34 and a VL sequence of SEQ ID NO: 39;

d. a VH sequence of SEQ ID NO: 34 and a VL sequence of SEQ ID NO: 40;

e. a VH sequence of SEQ ID NO: 35 and a VL sequence of SEQ ID NO: 38;

f. a VH sequence of SEQ ID NO: 36 and a VL sequence of SEQ ID NO: 41;

g. a VH sequence of SEQ ID NO: 36 and a VL sequence of SEQ ID NO: 40;

h. a VH sequence of SEQ ID NO: 37 and a VL sequence of SEQ ID NO: 41;

i. a VH sequence of SEQ ID NO: 37 and a VL sequence of SEQ ID NO: 38; or

j. a VH sequence of SEQ ID NO: 37 and a VL sequence of SEQ ID NO: 39,

preferably wherein A, the antibody or fragment thereof, comprises:

a. the heavy chain sequence of SEQ ID NO: 46 and light chain sequence of SEQ ID NO: 51;

b. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 51;

c. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 52;

d. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 53;

e. the heavy chain sequence of SEQ ID NO: 48 and light chain sequence of SEQ ID NO: 51;

f. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 54;

g. the heavy chain sequence of SEQ ID NO: 49 and light chain sequence of SEQ ID NO: 53;

h. the heavy chain sequence of SEQ ID NO: 50 and light chain sequence of SEQ ID NO: 54;

i. the heavy chain sequence of SEQ ID NO: 50 and light chain sequence of SEQ ID NO: 51; or

j. the heavy chain sequence of SEQ ID NO: 50 and light chain sequence of, SEQ ID NO: 52

or versions thereof with an engineered Fc domain.

14. A method of producing an antibody-drug conjugate according to any of claims 1 to ~~19~~13, wherein the method comprises the following steps:

a. providing A, an antibody or fragment thereof with an oligopeptide linker element preferably at its C-terminus, optionally preceded by a spacer element at the antibody light and/or heavy chains,
b. providing one or more toxins T with a non-cleavable linker element, and
c. conjugating the antibody and the toxin resulting in the antibody-drug conjugate.

15. An antibody-drug conjugate consisting of:

- the antibody consisting of two heavy chains of the amino acid sequence according to SEQ ID NO: 46, and two light chains of the amino acid sequence according to SEQ ID NO: 51, wherein the antibody binds to CLDN18.2,
- the linker [GGGGS]-[LPQTGG]-[ethylenediamine] at the C-terminus of the light chains, and
- the anthracycline-based small molecule toxin 3’-deamino-3’’,4’-anhydro-[2’’(S)-methoxy-3’’(R)-oxy-4’’-morpholinyl]doxorubicin (PNU-159682), linked covalently to the ethylenediamine of the linker at C_{13}, resulting in the loss of C_{14} and of the hydroxyl group; or
- the antibody consisting of two heavy chains of the amino acid sequence according to SEQ ID NO: 133, and two light chains of the amino acid sequence according to SEQ ID NO: 51, wherein the antibody binds to CLDN18.2,

- the linker [GGGGS]-[LPQTGG]-[ethylenediamine] at the C-terminus of the light chains, and
- the anthracycline-based small molecule toxin 3’-deamino-3’’,4’-anhydro-[2’’(S)-methoxy-3’’(R)-oxy-4’’-morpholinyl]doxorubicin (PNU-159682), linked covalently to the ethylenediamine of the linker at $C_{13,}$ resulting in the loss of C_{14} and of the hydroxyl group; or

- the antibody consisting of two heavy chains of the amino acid sequence according to SEQ ID NO: 134 and two light chains of the amino acid sequence according to SEQ ID NO: 51, wherein the antibody binds to CLDN18.2,
- the linker [GGGGS]-[LPQXTGG]-[ethylenediamine] at the C-terminus of the light chains, and
- the anthracycline-based small molecule toxin 3’-deamino-3’’,4’-anhydro-[2’’(S)-methoxy-3’’(R)-oxy-4’’-morpholinyl]doxorubicin (PNU-159682), linked covalently to the ethylenediamine of the linker at $C_{13,}$ resulting in the loss of C_{14} and of the hydroxyl group.

16. A pharmaceutical composition comprising the antibody-drug conjugate of any of claims 1 to 15 and an excipient.

17. The antibody-drug conjugate of any of claims 1 to 15 for use in ~~treatment~~ therapy.

18. ~~The~~ Use of the antibody-drug conjugate of any of claims 1 to 15 ~~for use~~ in the manufacture of a medicament for the treatment of cancer, preferably wherein the cancer is selected from pancreatic, gastric, esophageal, ovarian, and lung cancer.