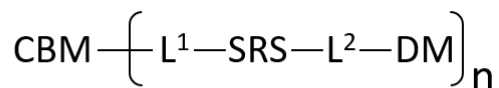
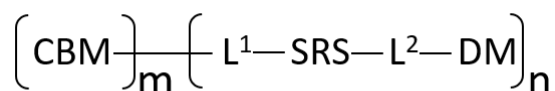


We claim:

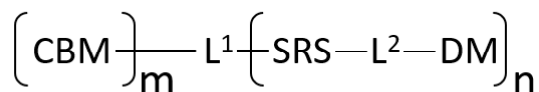
1. A binder-drug conjugate represented by any one of the formula:



or



or

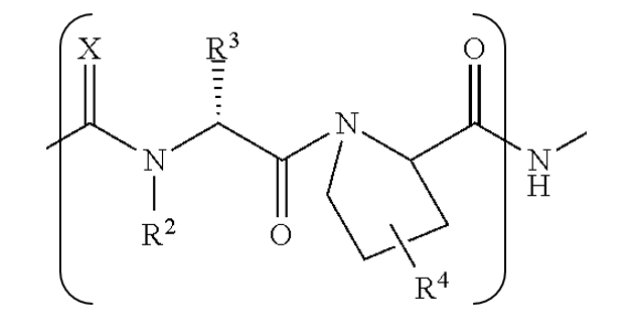


wherein

CBM represents a cell binding moiety that binds to a CTLA-4 receptor on a target cell in a disease state of a tissue, which cell surface feature undergoes slow internalization when bound by the binder-drug conjugate;

L¹ represents a spacer or a bond;

SRS represents a substrate recognition sequence cleaved by fibroblast activating protein alpha (FAP α) and represented by



wherein

R² represents H or a (C₁-C₆) alkyl, and preferably is H;

R³ represents H or a (C₁-C₆) alkyl, preferably is methyl, ethyl, propyl, or isopropyl, and more preferably methyl;

R⁴ is absent or represents a (C₁-C₆) alkyl, —OH, —NH₂, or halogen;

X represents O or S;

—NH— represents an amine that is part of L² if L² is a self immolative linker or part of DM if L² is a bond;

L² represents a self immolative linker that is cleavable by an enzyme present extracellularly in the disease tissue, wherein in the presence of the enzyme the linker moiety can be cleaved and releases the free drug moiety or a bond;

DM represents an immune activating agent;

m represents an integer from 1 to 6; and

n represents an integer from 1 to 500, more preferably 1 to 100, 1 to 10 or 1 to 5.

~~comprising: (i) a cell binding moiety that binds to a cell surface feature on a target cell in a disease state of a tissue, which cell surface feature undergoes slow internalization when bound by the binder drug conjugate; (ii) a drug moiety that has a pharmacological effect on bystander cells proximate to the target cell, which drug moiety has an EC₅₀ for the pharmacological effect which is attenuated by at least 10 fold when part of the binder drug conjugate relative to a free drug moiety released from the binder drug conjugate; and (iii) a linker moiety covalently linking the polypeptide binder moiety to the drug moiety, which linker moiety includes a substrate recognition sequence that is cleavable by an enzyme present extracellularly in the disease tissue, wherein in the presence of the enzyme the linker moiety can be cleaved and releases the free drug moiety.~~

2. The binder-drug conjugate of claim 1, wherein the disease tissue is a tumor.
3. The binder-drug conjugate of claim 1 or 2, wherein the target cell is a tumor cell.

4. The binder-drug conjugate of claim 1 or 2, wherein the target cell is a macrophage, monocyte derived suppressor cell (MDSC), dendritic cell, ~~fibroblast~~fibroblast, T-cell, NK cell, Mast Cell, Granulocyte, Eosinophil, B-cell or vascular endothelial cell.

5. The binder-drug conjugate of any one of claims 1-4, wherein the binder-drug conjugate, when bound with the surface feature on the target cell has an internalization half-time of at least 6 hours, more preferably at least 10, 12, 14, 16, 18, 20, 24, 36, 48 or 60 hours.

~~6. The binder drug conjugate of any one of claims 1-5, wherein the cell surface feature is a protein selectively expressed by the target cell in the disease tissue relative to normal cells from a healthy state of the tissue.~~

~~7. The binder drug conjugate of claim 2, 3, or 4, wherein the cell surface feature is a checkpoint protein or a co-stimulatory receptor.~~

~~8. The binder drug conjugate of claim 7, wherein the surface feature is a checkpoint protein selected from the group consisting of CTLA-4, PD-1, LAG-3, BTLA, KIR, TIM-3, PD-L1, PD-L2, B7-H3, B7-H4, HVEM, GAL9, CD160, VISTA, BTNL2, TIGIT, PVR, BTN1A1, BTN2A2, BTN3A2 and CSF-1R, more preferably CTLA-4, PD-1, LAG-3, TIM-3, BTLA, VISTA, HVEM, TIGIT, PVR, PD-L1 and CD160, and the binder moiety is a checkpoint antagonist.~~

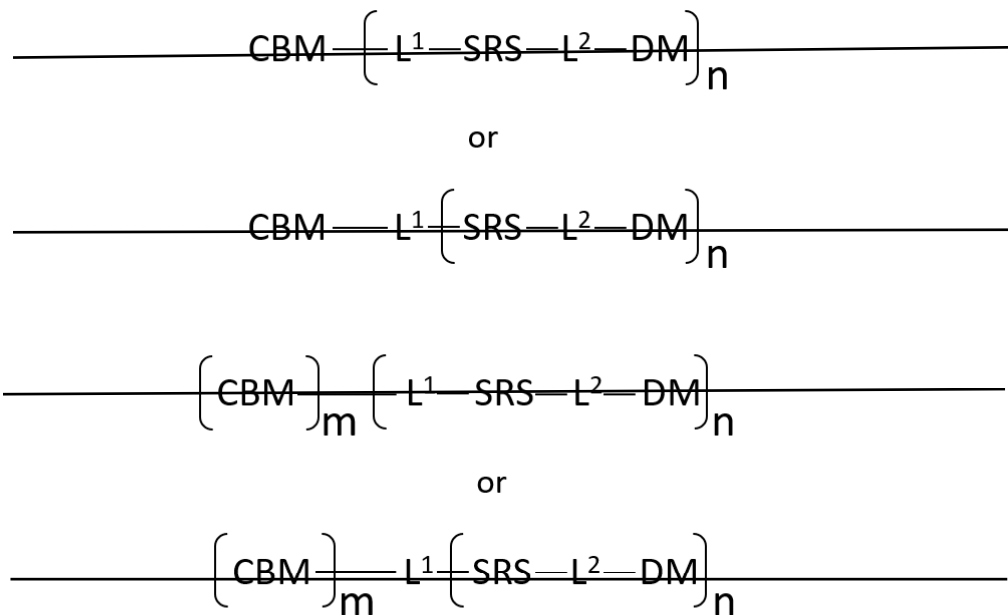
~~9. The binder drug conjugate of claim 7, wherein the surface feature is a costimulatory receptor or ligand selected from the group consisting of 4-1BB, 4-1BB-L, OX40, OX40-L, GITR, CD28, CD40, CD40-L, ICOS, ICOS-L, LIGHT, and CD27, more preferably 4-1BB, OX40, GITR, CD40 and ICOS, and the binder moiety is a costimulatory agonist.~~

~~106.~~ The binder-drug conjugate of any claims 1-~~95~~, wherein the cell binding moiety is an antibody, such humanized antibody, human antibody, or chimeric antibody, or comprises an antigen-binding portion thereof that binds the cell surface feature, such as Fab, F(ab)₂, F(ab')₂, F(ab')₃, Fd, Fv, disulfide linked Fv, dAb or sdAb (or nanobody), CDR, scFv, (scFv)₂, di-scFv, bi-scFv, tascFv (tandem scFv), AVIBODY (e.g., diabody, triabody, tetrabody), T-cell engager (BiTE), scFv-Fc, Fcab, mAb₂, small modular immunopharmaceutical (SMIP), Genmab

/ unibody or duobody, V-NAR domain, IgNAR, minibody, IgGACH2, DVD- Ig, probbody, intrabody, or a multispecificity antibody.

117. The binder-drug conjugate of any claims 1-95, wherein the binder moiety is non-antibody scaffold, such as selected from the group consisting of Affibodies, Affimers, Affilins, Anticalins, Atrimers, Avimer, DARPins, FN3 scaffolds (e.g. Adnectins and Centyrins), Fynomers, Kunitz domains, Nanofitin, Pronectins, OBodies, tribodies, Avimers, bicyclic peptides and Cys-knots.

12. ~~The binder drug conjugate of any of the preceding claims, represented by one of the formula~~



wherein

~~CBM represents a cell binding moiety which may be the same or different for each occurrence;~~

~~L¹ represents a spacer or a bond;~~

~~SRS represents a substrate recognition sequence;~~

~~L² represents a self immolative linker or a bond;~~

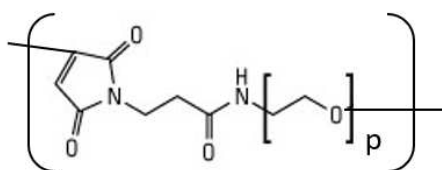
~~DM represents a drug moiety;~~

~~m represents an integer from 1 to 6; and~~

~~n represents an integer from 1 to 500, more preferably 1 to 100, 1 to 10 or 1 to 5.~~

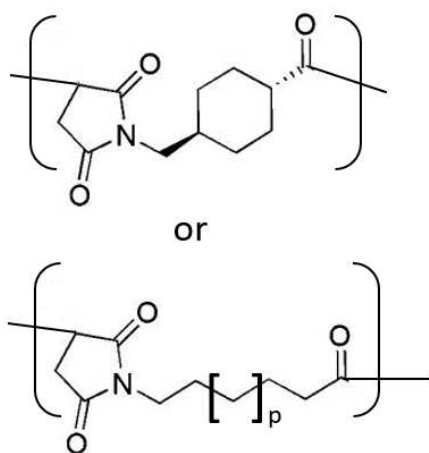
438. The binder-drug conjugate of ~~claim 12~~any one of claims 1-7, wherein L¹ is a hydrocarbon (straight chain or cyclic) such as 6-maleimidocaproyl, maleimidopropanoyl and maleimidomethyl cyclohexane-1-carboxylate, or L¹ is N-Succinimidyl 4-(2-pyridylthio) pentanoate, N- Succinimidyl 4-(N-maleimidomethyl) cyclohexane-1 carboxylate, N-Succinimidyl (4-iodo-acetyl) aminobenzoate, or L¹ is a polyether such as a poly(ethylene glycol).

449. The binder-drug conjugate of any one of claims 1-7 of claim 12, wherein CBM ~~includes~~ comprises a thiol, and L¹ is a poly(ethylene glycol) coupled to the thiol group through a maleimide moiety, L¹ being represented in the formula



wherein, p represents an integer from 1 to 100, preferably 6 to 50, more preferably 6 to 12.

~~45~~10. The binder-drug conjugate of any one of claims 1-7~~of claim 12~~, wherein CBM includes a thiol, and L¹ is a hydrocarbon moiety coupled to the thiol group through a maleimide moiety, L¹ being represented in the formula



wherein p represents an integer from 1 to 20, preferably 1 to 4.

~~16. — The binder drug conjugate of any of the preceding claims, wherein the substrate recognition sequence is cleaved by a protease, preferably a serine protease, metal protease or cysteine protease.~~

~~17. — The binder drug conjugate of claim 16, wherein the protease is present extracellularly in the disease state of the tissue in a patient at levels at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90 or even 100 times greater than the healthy state of the tissue in a patient.~~

~~18. — The binder drug conjugate of claim 16, wherein the protease is present extracellularly in the disease state of the tissue in a patient at levels at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90 or even 100 times greater than other tissue of the patient.~~

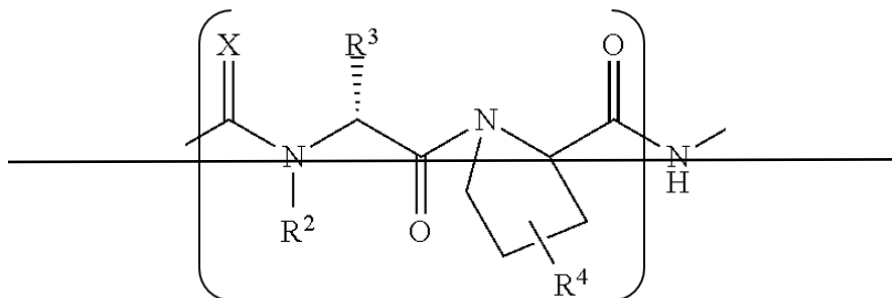
~~19. — The binder drug conjugate of any one of claims 1–18, wherein protease is a matrix metalloproteinase, selected from membrane bound matrix metalloproteinases (such as MMP14–17 and MMP24–25) and secreted matrix metalloproteinases (such as MMP1–13 and MMP18–23 and MMP26–28), preferably being MMP1, MMP2, MMP3, MMP4, MMP9, MMP11, MMP13, MMP14, MMP17 or MMP19, more preferably MMP2, MMP9 or MMP14.~~

~~20. — The binder drug conjugate of any one of claims 1–18, wherein protease an A Disintegrin and Metalloproteinase (ADAM), or an A Disintegrin or Metalloproteinase with Thrombospondin Motifs (ADAMTS).~~

~~21. — The binder drug conjugate of any one of claims 1–18, wherein protease a legumain, a matriptase (MT-SP1), a neutrophil elastase, a TMPRSS, a thrombin, a u-type plasminogen activator (uPA, also referred to as urokinase), PSMA or CD10 (CALLA).~~

~~22. — The binder drug conjugate of any one of claims 1–18, wherein protease is a post-proline cleaving protease, such as fibroblast activating protein alpha (FAP α).~~

~~23. — The binder drug conjugate of any one of claims 12–15, wherein substrate recognition sequence is cleaved by fibroblast activating protein alpha (FAP α) and represented by~~



wherein

R^2 represents H or a (C₁-C₆) alkyl, and preferably is H;

R^3 represents H or a (C₁-C₆) alkyl, preferably is methyl, ethyl, propyl, or isopropyl, and more preferably methyl;

R^4 is absent or represents a (C₁-C₆) alkyl, —OH, —NH₂, or halogen;

X represents O or S; and

—NH— represents an amine that is part of L^2 if L^2 is a self immolative linker or part of DM if L^2 is a bond.

2411. The binder-drug conjugate of any one of claims 12-15, or 231-10, wherein L^2 is a self immolative linker selected from the group consisting of —NH—(CH₂)₄—C(=O)—, —NH—(CH₂)₃—C(=O)—, p-aminobenzyloxycarbonyl (PABC) and 2,4-bis(hydroxymethyl)aniline.

2512. The binder-drug conjugate of any one of claims 1-2411, wherein the pharmacological effect of the drug moiety is dependent on the free drug moiety being cell permeable, whereas when part of the binder-drug conjugate the drug moiety is substantially cell impermeable.

2613. The binder-drug conjugate of any one of claims 1-2411, wherein the pharmacological effect of the drug moiety is substantially attenuated by covalent linking to L^1 .

27. —The binder drug conjugate of any claims 1-26, wherein the drug moiety is an immunomodulator.

2814. The binder-drug conjugate of any one of claims 1-13 of claim 27, wherein the drug moiety is an immune activating agent.

~~29~~15. The binder-drug conjugate ~~of any one of claims 1-14~~of claim 27, wherein the free drug moiety induces an innate immunity pathway.

~~30~~16. The binder-drug conjugate of ~~any one of claims 1-15~~claim 27, 28, or 29, wherein the immunomodulator is an immuno-DASH inhibitor that inhibits the enzymatic activity of DPP8 and DPP9 and induces macrophage pyroptosis.

~~31~~17. The binder-drug conjugate of ~~claim 27, 28, or 29~~any one of claims 14-16, wherein the immune activating agent is a STING agonist.

~~32~~18. The binder-drug conjugate of ~~claim 27, 28, or 29~~any one of claims 14-16, wherein the immune activating agent is a RIG-1 agonist.

~~33~~19. The binder-drug conjugate ~~of any one of claims 14-16~~of claim 27, 28, or 29, wherein the immune activating agent is a Toll-like receptor (TLR) agonist, such as a selected from the group consisting of a TLR1/2 agonist, a TLR2 agonist, a TLR3 agonist, a TLR4 agonist, a TLR5 agonist, a TLR6/2 agonist, a TLR7 agonist, a TLR7/8 agonist, a TLR7/9 agonist, a TLR8 agonist, a TLR9 agonist, and a TLR11 agonist, preferably selected from the group consisting of a TLR3 agonist, a TLR7 agonist, a TLR7/8 agonist, and a TLR9 agonist.

~~34~~20. The binder-drug conjugate of any claims 1-~~26~~19, wherein the drug moiety is cytotoxic to cancer associated fibroblasts (CAFs).

~~35~~21. The binder-drug conjugate of any claims 1-~~20~~26, wherein the drug moiety polarizes tumor associated macrophage towards M1 macrophage or inhibits M2 macrophage immunosuppressive activity.

~~36~~22. The binder-drug conjugate of any claims 1-~~21~~26, wherein the drug moiety accelerates T-cell priming and/or dendritic cell trafficking.

~~37~~23. The binder-drug conjugate of any claims 1-~~22~~26, wherein the drug moiety inhibits or depletes Treg cells, such as by blocking immunosuppressive function or migration to lymph nodes and/or the tumor microenvironment.

~~38~~24. The binder-drug conjugate of any claims 1-~~26~~23, wherein the Therapeutic Index of the binder-drug conjugate is at least 5 times greater than the Therapeutic Index for the free drug moiety when given systemically, more preferably at least 10, 20, 30, 40, 50, 75 or even 100 times greater.

~~39~~25. The binder-drug conjugate ~~method of any of the preceding claims~~ any one of claims 1-24, wherein the immunomodulator is ~~the a~~ low-molecular weight inhibitor having a molecular weight less than 5000 amu, preferably less than 2500 amu.

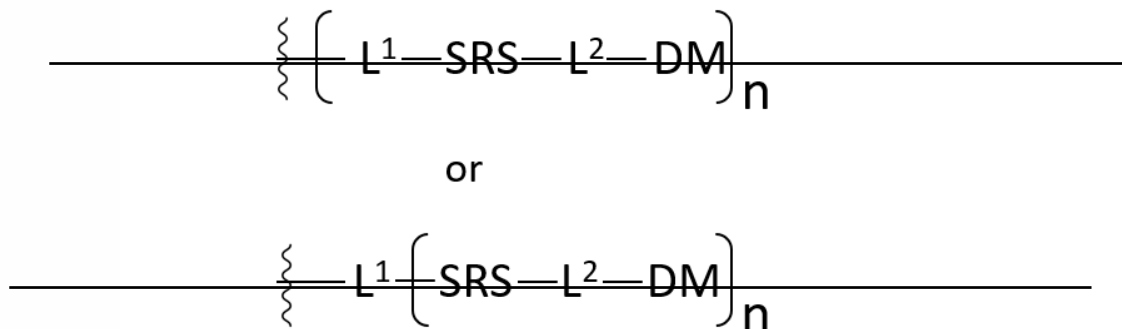
26. A pharmaceutical composition comprising the binder-drug conjugate of any one of claims 1-25; and a pharmaceutically acceptable excipient.

27. Use of the binder-drug conjugate of any one of claims 1-25 in the manufacture of a medicament for treating cancer.

28. The use of claim 27, wherein the cancer is acute myeloid leukemia (AML).

29. The use of claim 27 or 28, wherein the medicament is to be conjointly administered with a PGE2 inhibitor.

~~40. — A binder drug conjugate comprising a polypeptide including one or more affimer sequences that bind to a cell surface protein on cells in a tumor, and having one or more drug conjugate moieties appended thereto, which drug conjugate moieties are represented in the formulas~~



wherein

L¹ represents a spacer or a bond;

SRS represents a substrate recognition sequence for an extracellular protease which is expressed in the extracellular space of a tumor;

L² represents a self immolative linker or a bond;

DM represents a drug moiety;

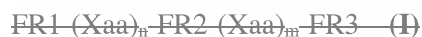
m represents an integer from 1 to 6, preferably 1, 2 or 3; and

n represents an integer from 1 to 500, more preferably 1 to 100, 1 to 10 or 1 to 5.

41. — The binder drug conjugate of claim 40, wherein the affimer sequence is a PD-L1 binding moiety.

42. — The binder drug conjugate of claim 41 wherein the PD-L1 binding moiety is affimer polypeptide sequence which binds to PD-L1 with a K_d of 1×10⁻⁶M or less and inhibits interaction of the PD-L1 to which it is bound with PD-1.

43. — The binder drug conjugate of claim 41 or 42, wherein the PD-L1 binding affimer polypeptide has an amino acid sequence represented in general formula (I)



wherein

FR1 is a polypeptide sequence represented by MIPGGLSEAK PATPEIQEIV DKVKPQLEEK

TNETYGKLEA VQYKTQVLA (SEQ ID No. 1) or a polypeptide sequence having at least 70% homology thereto;

FR2 is a polypeptide sequence represented by GTNYYIKVRA GDNKYMHLKV FKSL (SEQ ID No. 2)

or a polypeptide sequence having at least 70% homology thereto;

FR3 is a polypeptide sequence represented by EDLVLTGYQV DKNKDDELTG F (SEQ ID No. 3) or a polypeptide sequence having at least 70% homology thereto; and Xaa, individually for each occurrence, is an amino acid residue; and n and m are each, independently, an integer from 3 to 20.

44. — The binder drug conjugate of claim 41 or 42, wherein the PD L1 binding affimer polypeptide has an amino acid sequence represented in the general formula:

MIP-Xaa1-

GLSEAKPATPEIQEIVDKVKPQLEEKTNETYGKLEAVQYKTQVLA (Xaa)_n-Xaa2-TNYYIKVRAGDNKYMHLKVF-Xaa3-Xaa4-Xaa5-(Xaa)_m-Xaa6-D-Xaa7-VLTGYQVDKNKDDELTGF (SEQ ID No. 4)

wherein

Xaa, individually for each occurrence, is an amino acid residue;

n and m are each, independently, an integer from 3 to 20;

Xaa1 is Gly, Ala, Val, Arg, Lys, Asp, or Glu;

Xaa2 is Gly, Ala, Val, Ser or Thr;

Xaa3 is Arg, Lys, Asn, Gln, Ser, or Thr;

Xaa4 is Gly, Ala, Val, Ser or Thr;

Xaa5 is Ala, Val, Ile, Leu, Gly or Pro;

Xaa6 is Gly, Ala, Val, Asp or Glu; and

Xaa7 is Ala, Val, Ile, Leu, Arg or Lys.

45. — The binder drug conjugate of claim 41 or 42, wherein the PD L1 binding affimer polypeptide has an amino acid sequence represented in the general formula:

MIPRGLSEAKPATPEIQEIVDKVKPQLEEKTNETYGKLEAVQYKTQVLA-(Xaa)_n-STNYYIKVRAGDNKYMHLKVFNGP-(Xaa)_m-ADRVLTGYQVDKNKDDELTGF (SEQ ID No. 5)

wherein

Xaa, individually for each occurrence, is an amino acid residue; and

n and m are each, independently, an integer from 3 to 20.

46. — The protein of any of the preceding claims, wherein the the the PD-L1 binding-affimer polypeptide has an amino acid sequence selected from SEQ ID Nos. 76 to 84, or an amino acid sequence having at least 70% homology thereto.

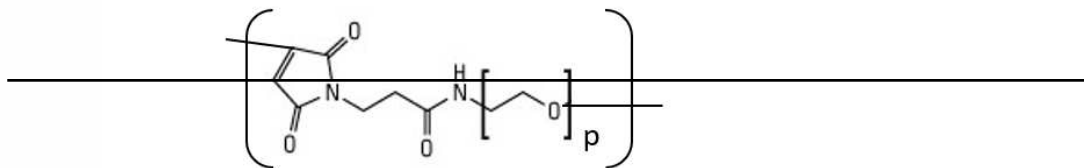
47. — The binder drug conjugate of any one of claims 41 to 46, wherein at least on drug-conjugate moiety appended to the affimer sequence through the thiol side chain of cysteine introduced into the affimer sequence, preferably in a portion of the affimer sequence regions corresponding to FR1, FR2 and/or FR3.

48. — The binder drug conjugate of any one of claims 41 to 47, wherein the affimer binding to PD-L1 (a) increases T cell proliferation in a mixed lymphocyte reaction (MLR) assay; (b) increases interferon γ production in an MLR assay; and/or (c) increases interleukin-2 (IL-2) secretion in an MLR assay.

49. — The binder drug conjugate of any one of claims 41 to 48, wherein the affimer is part of a fusion protein comprising a half-life extending polypeptide moieties selected from the group consisting of an Fc domain or portion thereof, an albumin protein or portion thereof, an albumin-binding polypeptide moiety, transferrin or portion thereof, a transferrin-binding polypeptide moiety, fibronectin or portion thereof, or a fibronectin-binding polypeptide moiety.

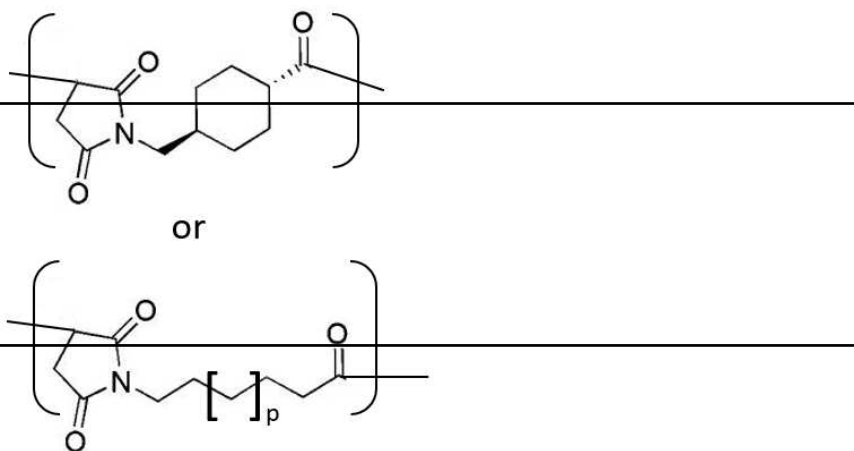
50. — The binder drug conjugate of any one of claims 41-49, wherein L^+ is a hydrocarbon (straight chain or cyclic) such as 6-maleimidocaproyl, maleimidopropanoyl and maleimidomethyl cyclohexane-1-carboxylate, or L^+ is N-Succinimidyl 4-(2-pyridylthio) pentanoate, N-Succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, N-Succinimidyl (4-iodo-acetyl) aminobenzoate, or L^+ is a polyether such as a poly(ethylene glycol).

51. — The binder drug conjugate of claim 50, wherein the affimer includes a cysteine with a free thiol, and L^+ is a poly(ethylene glycol) coupled to the thiol group through a maleimide moiety, L^+ being represented in the formula



wherein p represents an integer from 1 to 100, preferably 6 to 50, more preferably 6 to 12.

52. — The binder drug conjugate of claim 50, wherein the affimer includes a cysteine with a free thiol, and L^+ is a hydrocarbon moiety coupled to the thiol group through a maleimide moiety, L^+ being represented in the formula



wherein p represents an integer from 1 to 20, preferably 1 to 4.

53. — The binder drug conjugate of any of the preceding claims 41-52, wherein the substrate recognition sequence is cleaved by a serine protease, a metal protease or cysteine protease.

54. — The binder drug conjugate of claim 53, wherein the protease is present extracellularly in the tumor tissue in a patient at levels at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90 or even 100 times greater than the non-tumor tissue in a patient.

55. — The binder drug conjugate of claim 53, wherein the protease is present extracellularly in the tumor tissue in a patient at levels at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90 or even 100 times greater than other tissue of the patient.

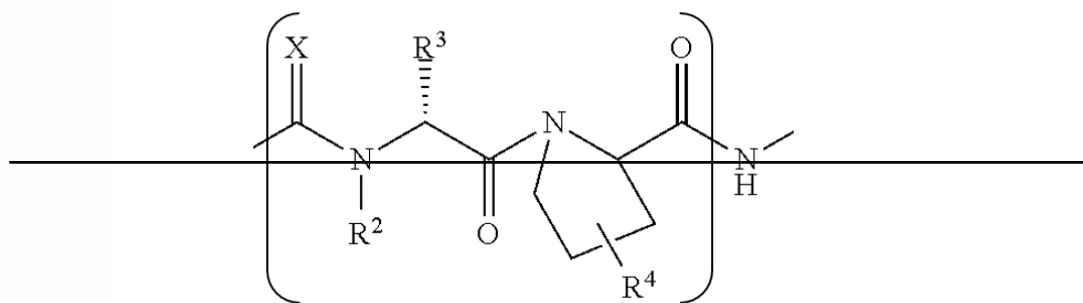
56. — The binder drug conjugate of any one of claims 41-55, wherein protease is a matrix metalloproteinase, selected from membrane bound matrix metalloproteinases (such as MMP14-17 and MMP24-25) and secreted matrix metalloproteinases (such as MMP1-13 and MMP18-23 and MMP26-28), preferably being MMP1, MMP2, MMP3, MMP4, MMP9, MMP11, MMP13, MMP14, MMP17 or MMP19, more preferably MMP2, MMP9 or MMP14.

57. — The binder drug conjugate of any one of claims 41-55, wherein protease is an A Disintegrin and Metalloproteinase (ADAM), or an A Disintegrin or Metalloproteinase with Thrombospondin Motifs (ADAMTS).

58. — The binder drug conjugate of any one of claims 41-55, wherein protease is a legumain, a matriptase (MT SP1), a neutrophil elastase, a TMPRSS, a thrombin, a u type plasminogen activator (uPA, also referred to as urokinase), PSMA or CD10 (CALLA).

59. — The binder drug conjugate of any one of claims 41-55, wherein protease is a post-proline cleaving protease, such as fibroblast activating protein alpha (FAP α).

60. — The binder drug conjugate of any one of claims 41-55, wherein substrate recognition sequence is cleaved by fibroblast activating protein alpha (FAP α) and represented by



wherein

R² represents H or a (C₁-C₆) alkyl, and preferably is H;

R³ represents H or a (C₁-C₆) alkyl, preferably is methyl, ethyl, propyl, or isopropyl, and more preferably methyl;

R⁴ is absent or represents a (C₁-C₆) alkyl, —OH, —NH₂, or halogen;

X represents O or S; and

—NH— represents an amine that is part of L² if L² is a self immolative linker or part of DM if L² is a bond.

61. — The binder drug conjugate of any one of claims 41-55 or 60, wherein L² is a self immolative linker selected from the group consisting of —NH—(CH₂)₄—C(=O)—, —NH—(CH₂)₃—C(=O)—, p-aminobenzyloxycarbonyl (PABC) and 2,4-bis(hydroxymethyl)aniline.

~~62. — The binder drug conjugate of any one of claims 41–61, wherein the pharmacological effect of the drug moiety is dependent on the free drug moiety being cell permeable, whereas when part of the binder drug conjugate the drug moiety is substantially cell impermeable.~~

~~63. — The binder drug conjugate of any one of claims 41–61, wherein the pharmacological effect of the drug moiety is substantially attenuated by covalent linking to L⁺.~~

~~64. — The binder drug conjugate of any claims 41–61, wherein the drug moiety is an immunomodulator.~~

~~65. — The binder drug conjugate of claim 64, wherein the drug moiety is an immune activating agent.~~

~~66. — The binder drug conjugate of claim 64, wherein the free drug moiety induces an innate immunity pathway.~~

~~67. — The binder drug conjugate of any one of claims 64–66, wherein the immunomodulator is an immuno DASH inhibitor that inhibits the enzymatic activity of DPP8 and DPP9 and induces macrophage pyroptosis.~~

~~68. — The binder drug conjugate of any one of claims 64–66, wherein the immunomodulator is a STING agonist.~~

~~69. — The binder drug conjugate of any one of claims 64–66, wherein the immunomodulator is a RIG-1 agonist.~~

~~70. — The binder drug conjugate of any one of claims 64–66, wherein the immunomodulator is a a Toll-like receptor (TLR) agonist, such as a selected from the group consisting of a TLR1/2 agonist, a TLR2 agonist, a TLR3 agonist, a TLR4 agonist, a TLR5 agonist, a TLR6/2 agonist, a TLR7 agonist, a TLR7/8 agonist, a TLR7/9 agonist, a TLR8 agonist, a TLR9 agonist, and a TLR11 agonist, preferably selected from the group consisting of a TLR3 agonist, a TLR7 agonist, a TLR7/8 agonist, and a TLR9 agonist.~~

~~71. — The binder drug conjugate of any claims 41–61, wherein the drug moiety is cytotoxic to cancer associated fibroblasts (CAFs).~~

~~72. — The binder drug conjugate of any claims 41–61, wherein the drug moiety polarizes tumor associated macrophage towards M1 macrophage or inhibits M2 macrophage immunosuppressive activity.~~

~~73. — The binder drug conjugate of any claims 41–61, wherein the drug moiety accelerates T cell priming and/or dendritic cell trafficking.~~

~~74. — The binder drug conjugate of any claims 41–61, wherein the drug moiety inhibits or depletes Treg cells, such as by blocking immunosuppressive function or migration to lymph nodes and/or the tumor microenvironment.~~

~~75. — The binder drug conjugate of any claims 41–61, wherein the Therapeutic Index of the binder drug conjugate is at least 5 times greater than the Therapeutic Index for the free drug moiety when given systemically, more preferably at least 10, 20, 30, 40, 50, 75 or even 100 times greater.~~

~~76. — The binder drug conjugate of any claims 41–75, wherein the immunomodulator is the low-molecular inhibitor having a molecular weight less than 5000 amu, preferably less than 2500 amu.~~

~~77. — An combination PD-L1 inhibitor/innate immunity stimulator comprising a PD-L1 binding polypeptide and a drug moiety conjugated thereto which is a sterile inducer of a innate immune response (such as an immuno-DASH inhibitor, STING agonist, TRL7/8 agonist or RIG-1 agonist), wherein the PD-L1 binding polypeptide causes accumulation of the PD-L1 inhibitor/innate stimulator in tumors relative to other tissue of a patient, and wherein the drug moiety is selectively released from the PD-L1 binding polypeptide in the tumor microenvironment relative to other tissue of a patient.~~

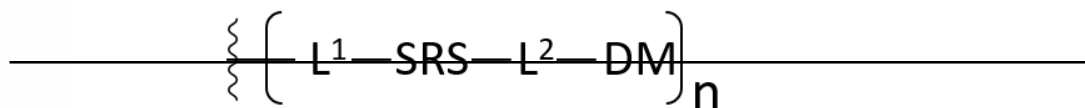
~~78. — A pharmaceutical preparation suitable for therapeutic use in a human patient, comprising (i) a binder drug conjugate any of claims 1–76 or a combination PD-L1 inhibitor/innate stimulator of claim 77, and (ii) one or more pharmaceutically acceptable excipients, buffers, salts or the like.~~

~~79. — Use of the pharmaceutical preparation of claim 78 as part of a treatment for a patient suffering cancer.~~

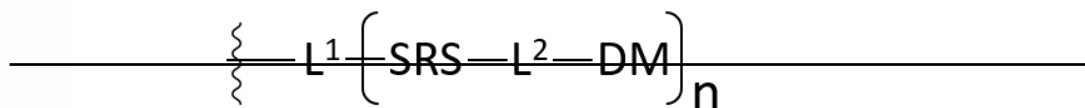
~~80. — The use of the pharmaceutical preparation of claim 79, wherein the treatment includes administering a PGE2 inhibitor to the patient.~~

81. — A binder drug conjugate for killing AML cells comprising: i) a cell binding moiety that binds to a cell surface feature selectively expressed on AML cells (such as CD33 or CD123), which cell surface feature is internalized by AML cells when bound by the binder drug conjugate; (ii) an immuno-DASH inhibitor moiety, which when released from the conjugate as a free immuno-DASH inhibitor, is toxic to the AML cells; and (iii) a linker moiety covalently linking the cell binding moiety to the I DASH Inhibitor moiety, which linker moiety includes a substrate recognition sequence that is cleavable by an enzyme present intracellular in the AML cells (such as cathepsin), wherein internalization of the binder drug conjugate by AML cells upon binding the cell surface feature results in exposure of the linker moiety to the of the intracellular enzyme and cleavage of the linker moiety and intracellular release the free immuno-DASHG moiety in the AML cells.

82. — A binder drug conjugate comprising an AML cell binding moiety (such as a CD33 binder or CD123 binder), and having one or more drug conjugate moieties appended thereto, which drug conjugate moieties are represented in the formulas



or



wherein

L^1 represents a spacer or a bond;

SRS represents a substrate recognition sequence for an intracellular protease which is expressed in the AML cells;

L^2 represents a self immolative linker or a bond;

DM represents an immuno-DASH inhibitor moiety;

m represents an integer from 1 to 6, preferably 1, 2 or 3; and

n represents an integer from 1 to 500, more preferably 1 to 100, 1 to 10 or 1 to 5.

83. — A pharmaceutical preparation suitable for therapeutic use in human patients as part of a treatment for AML, comprising (i) a binder drug conjugate any of claim 80 or 18, and (ii) one or more pharmaceutically acceptable excipients, buffers, salts or the like.

84. ~~Use of the pharmaceutical preparation of claim 82 as part of a treatment for a patient suffering~~
~~AML.~~