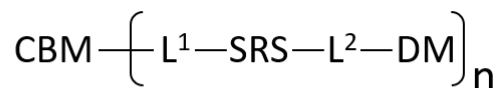
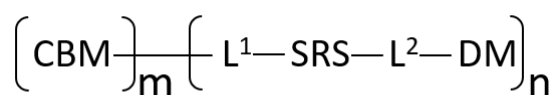


We claim:

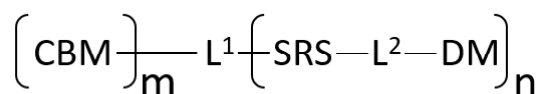
1. A binder-drug conjugate represented by any one of the formula:



or



or

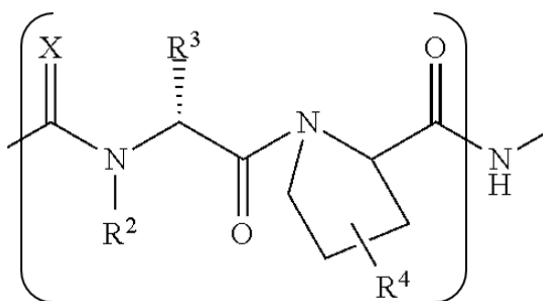


wherein

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;

L^1 represents a spacer or a bond;

SRS represents a substrate recognition sequence cleaved by fibroblast activating protein alpha ($\text{FAP}\alpha$) and represented by



wherein

R^2 represents H or a (C_1 - C_6) alkyl, and preferably is H;

R^3 represents H or a (C_1 - C_6) alkyl, preferably is methyl, ethyl, propyl, or isopropyl, and more preferably methyl;

R^4 is absent or represents a (C_1 - C_6) alkyl, —OH, —NH₂, or halogen;

X represents O or S;

—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;

L^2 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.

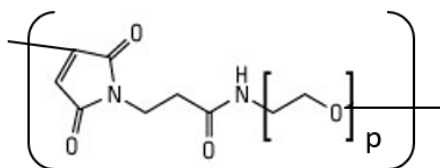
2. The binder-drug conjugate of claim 1, wherein the disease tissue is a tumor.
3. The binder-drug conjugate of claim 1 or 2, wherein the target cell is a tumor cell.
4. The binder-drug conjugate of claim 1 or 2, wherein the target cell is a macrophage, monocyte derived suppressor cell (MDSC), dendritic cell, fibroblast, 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 claims 1-5, 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')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, probody, intrabody, or a multispecificity antibody.

7. The binder-drug conjugate of any claims 1-5, 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.

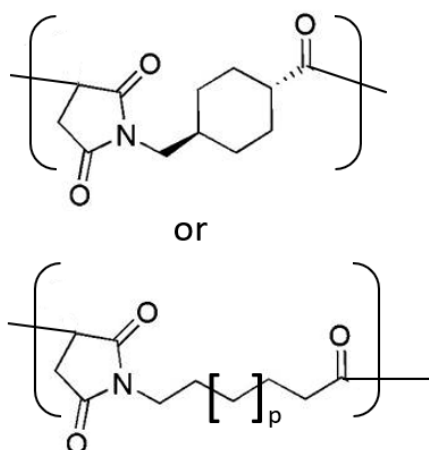
8. The binder-drug conjugate of any one of claims 1-7, wherein L¹ is a hydrocarbon (straight chain or cyclic) such as 6-maleimidocaproyl, maleimidopropanoyl and maleimidomethyl cyclohexane-1-carboxylate, or L¹ is N-Succinimidyl 4-(2-pyridylthio) pentanoate, N- Succinimidyl 4-(N-maleimidomethyl) cyclohexane-1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

9. The binder-drug conjugate of any one of claims 1-7, wherein CBM 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.

10. The binder-drug conjugate of any one of claims 1-7, 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.

11. The binder-drug conjugate of any one of claims 1-10, wherein L^2 is a self immolative linker selected from the group consisting of $-\text{NH}-(\text{CH}_2)_4-\text{C}(=\text{O})-$, $-\text{NH}-(\text{CH}_2)_3-\text{C}(=\text{O})-$, p-aminobenzyloxycarbonyl (PABC) and 2,4-bis(hydroxymethyl)aniline.
12. The binder-drug conjugate of any one of claims 1-11, 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.
13. The binder-drug conjugate of any one of claims 1-11, wherein the pharmacological effect of the drug moiety is substantially attenuated by covalent linking to L^1 .
14. The binder-drug conjugate of any one of claims 1-13, wherein the drug moiety is an immune activating agent.
15. The binder-drug conjugate of any one of claims 1-14, wherein the free drug moiety induces an innate immunity pathway.

16. The binder-drug conjugate of any one of claims 1-15, wherein the immunomodulator is an immuno-DASH inhibitor that inhibits the enzymatic activity of DPP8 and DPP9 and induces macrophage pyroptosis.
17. The binder-drug conjugate of any one of claims 14-16, wherein the immune activating agent is a STING agonist.
18. The binder-drug conjugate of any one of claims 14-16, wherein the immune activating agent is a RIG-1 agonist.
19. The binder-drug conjugate of any one of claims 14-16, 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.
20. The binder-drug conjugate of any claims 1-19, wherein the drug moiety is cytotoxic to cancer associated fibroblasts (CAFs).
21. The binder-drug conjugate of any claims 1-20, wherein the drug moiety polarizes tumor associated macrophage towards M1 macrophage or inhibits M2 macrophage immunosuppressive activity.
22. The binder-drug conjugate of any claims 1-21, wherein the drug moiety accelerates T-cell priming and/or dendritic cell trafficking.
23. The binder-drug conjugate of any claims 1-22, 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.

24. The binder-drug conjugate of any claims 1-23, 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.
25. The binder-drug conjugate of any one of claims 1-24, wherein the immunomodulator is 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.