

WHAT IS CLAIMED IS:

1. A bi-functional therapeutic suitable for treating cancer comprising:
a targeting component which targets a tumor-associated antigen and
an enzyme which, when delivered to a tumor by said targeting component,
enzymatically converts the tumor phenotype to that of an incompatible allograft or xenograft,
said enzyme being coupled to said targeting component.
2. The bi-functional therapeutic according to claim 1, wherein the tumor-associated antigen is selected from the group consisting of FOLH1/PSMA, VEGFR, CD19, CD20, CD25, CD30, CD33, CD38, CD52, B cell Maturation Antigen (BCMA), CD79, Somatostatin receptor, 5T4, gp100, CEA, melan A/MART-1, MAGE, NY-ESO-1, PSA, tyrosinase, HER-2, HER-3, EGFR, hTERT, MUC1, mesothelin, Nectin-4, TROP-2, Tissue Factor, and CA-125.
3. The bi-functional therapeutic according to claim 1 or claim 2, wherein the targeting component is selected from the group consisting of an antibody or antigen-binding fragment thereof, a protein, a peptide, an aptamer and a small molecule ligand.
- ~~4. The bi-functional therapeutic according to claim 3, wherein the targeting component is a peptide linked to the enzyme via a peptide bond.~~
- ~~5.4.~~ The bi-functional therapeutic according to claim ~~43~~, wherein the targeting component is an antibody or antigen-binding derivative or fragment thereof.
- ~~6.5.~~ The bi-functional therapeutic according to anyone of claims 1-4, wherein the targeting component and the enzyme are genetically engineered to produce a fusion protein, or wherein the targeting component and the enzyme are chemically linked.
- ~~7. The bi-functional therapeutic according to claim 1, wherein the targeting component and the enzyme are chemically linked.~~

~~8. The bi-functional therapeutic according to claim 3, wherein the targeting component is a small molecule ligand chemically linked to the enzyme with an intervening polyethylene glycol (PEG) spacer.~~

9.6. The bi-functional therapeutic according to claim 8~~1~~, wherein the targeting component is ACUPA [2-(3-((S)-5-Amino-1carboxypentyl)ureido)pentanedioic Acid] chemically linked to the enzyme with an intervening PEG spacer.

~~10.7. The bi-functional therapeutic according to any one of claims 1-6, wherein the enzyme is an enzyme involved in post-translational modification and is selected from the group consisting of a transferase, and glycosyltransferase, and active portions thereof.~~

~~11. The bi-functional therapeutic according to claim 10, wherein the enzyme involved in post-translational modification is a transferase.~~

~~12. The bi-functional therapeutic according to claim 11, wherein the transferase is a glycosyltransferase.~~

~~13.8. The bi-functional therapeutic according to claim 12~~7~~, wherein the glycosyltransferase is selected from the group consisting of glycosyltransferase A (Alpha 1-3-N-Acetylgalactosaminyltransferase), glycosyltransferase B (alpha 1-3-galactosyltransferase), alpha-gal-transferase, glycosyltransferase A (Gly268Ala), and fucosyltransferase, and active portions thereof.~~

14.9. The bi-functional therapeutic according to any one of claims 1-8, wherein the enzyme comprises an appended second amino acid sequence at its C-terminus, optionally wherein the second amino acid sequence includes a cleavable amino acid sequence between the enzyme and the appended second sequence, optionally wherein the cleavable amino acid sequence is cleavable by PSA, matrix metalloproteinases, or cathepsin B.

~~15.~~ The bi-functional therapeutic according to claim ~~14~~, wherein the second amino acid sequence includes a cleavable amino acid sequence between the enzyme and the appended second sequence.

~~16.~~ The bi-functional therapeutic according to claim ~~15~~, wherein the cleavable amino acid sequence is cleavable by PSA, matrix metalloproteinases, or cathepsin B.

~~17.~~10. The bi-functional therapeutic according to any one of claims 1-9, wherein the tumor having the tumor-associated antigen expresses an H-antigen.

~~18.~~11. The bi-functional therapeutic according to any one of claims 1-10, wherein the tumor having the tumor-associated antigen is from a cancer selected from the group consisting of lung cancer, gastric cancer, colorectal cancer, breast cancer, prostate cancer, blood cancer, cervical cancer, endometrial cancer, ovarian cancer, bladder cancer, renal cancer, brain cancer, hepatic cancer, esophageal cancer, adrenal cancer, head and neck cancer, melanoma, and pancreatic cancer.

~~19.~~12. The bi-functional therapeutic according to claim ~~18~~11, wherein the cancer is prostate cancer.

~~20.~~13. The bi-functional therapeutic according to claim ~~19~~12, wherein the targeting component targets the prostate-specific membrane antigen (PSMA)/Folate hydrolase 1 (FOLH1) receptor.

~~21.~~14. The bi-functional therapeutic according to claim ~~19~~11 or claim 13, wherein the targeting component is a PSMA receptor antibody or derivative of a PSMA receptor antibody.

~~22.~~15. The bi-functional therapeutic according to claim ~~19~~14, wherein the targeting component is an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 28, and a light chain variable region comprising the amino

acid sequences of SEQ ID NO: 29; or selected from the group consisting of J591, J415, J533, and E99.

23.16. The bi-functional therapeutic according to claim ~~17~~11, wherein the cancer is breast cancer.

24.17. The bi-functional therapeutic according to claim ~~23~~16, wherein the targeting component targets an HER receptor family member.

25.18. The bi-functional therapeutic according to claim ~~24~~16 or claim ~~17~~, wherein the targeting component is ~~monoclonal~~an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 30, and a light chain variable region comprising the amino acid sequences of SEQ ID NO: 314~~45~~.

26.19. The bi-functional therapeutic according to claim ~~17~~11, wherein the cancer is a blood cancer of B-cell lineage.

27.20. The bi-functional therapeutic according to claim ~~26~~19, wherein the targeting component targets CD19.

28.21. The bi-functional therapeutic according to claim ~~27~~19 or claim ~~20~~, wherein the targeting component is the monoclonal antibody obexelimab or denintuzumab.

29.—~~A method of treating cancer, said method comprising:~~
~~selecting a subject having cancer;~~
~~providing a bi-functional therapeutic according to any of claims 1-28; and~~
~~administering, to the selected subject, the bi-functional therapeutic under~~
~~conditions effective to treat the cancer.~~

30.—~~The method according to claim 29, wherein the subject is a human.~~

31. — The method according to claim 29, wherein the tumor associated antigen is selected from the group consisting of FOLH1/PSMA, VEGFR, CD19, CD20, CD25, CD30, CD33, CD38, CD52, B Cell Maturation Antigen (BCMA), CD79, Somatostatin receptor, 5T4, gp100, CEA, melan A/MART-1, MAGE, NY-ESO-1, PSA, tyrosinase, HER-2, HER-3, EGFR, hTERT, MUC1, mesothelin, Nectin-4, TROP-2, Tissue Factor, and CA-125.

32. — The method according to claim 29, wherein the targeting component is selected from the group consisting of an antibody or binding fragment thereof, a protein, a peptide, and a small molecule.

33. — The method according to claim 32, wherein the targeting component is a peptide linked to the enzyme via a peptide bond.

34. — The method according to claim 32, wherein the targeting component is an antibody or antigen-binding derivative or fragment thereof.

35. — The method according to claim 29, wherein the targeting component and the enzyme are genetically engineered to produce a fusion protein.

36. — The method according to claim 29, wherein the targeting component and the enzyme are chemically linked.

37. — The method according to claim 29, wherein the targeting component is a small molecule/ligand chemically linked to the enzyme with an intervening polyethylene glycol (PEG) spacer.

38. — The method according to claim 37, wherein the targeting component is ACUPA [2-(3-((S)-5-Amino-1-carboxypentyl)ureido)pentanedioic Acid] chemically linked to the enzyme with an intervening PEG spacer.

39. — ~~The method according to claim 29, wherein the enzyme is an enzyme involved in post-translational modification and is selected from the group consisting of glycosylation, a transferase, and glycosyltransferase.~~

40. — ~~The method according to claim 39, wherein the enzyme involved in post-translational modification is a transferase.~~

41. — ~~The method according to claim 40, wherein the transferase is a glycosyltransferase.~~

42. — ~~The method according to claim 41, wherein the glycosyltransferase is selected from the group consisting of glycosyltransferase A, glycosyltransferase B, alpha-gal-transferase, glycosyltransferase A (Gly268Ala), and fucosyltransferase.~~

43. — ~~The method according to claim 29, wherein the enzyme comprises an appended second amino acid sequence at its C-terminus.~~

44. — ~~The method according to claim 43, wherein the second amino acid sequence comprises a cleavable amino acid sequence between the enzyme and the appended second sequence.~~

45. — ~~The method according to claim 44, wherein the cleavable amino acid sequence is cleavable by PSA, matrix metalloproteinases, or cathepsin B.~~

46. — ~~The method according to claim 29, wherein the cancer expresses an H-antigen.~~

47. — ~~The method according to claim 29, wherein the cancer is selected from the group consisting of lung cancer, gastric cancer, colorectal cancer, breast cancer, prostate cancer, blood cancer, cervical cancer, endometrial cancer, ovarian cancer, bladder cancer, renal cancer,~~

~~brain cancer, hepatic cancer, esophageal cancer, adrenal cancer, head and neck cancer, melanoma, and pancreatic cancer.~~

~~48.——The method according to claim 47, wherein the cancer is prostate cancer.~~

~~49.——The method according to claim 48, wherein the targeting component targets the prostate-specific membrane antigen (PSMA)/Folate hydrolase 1 (FOLH1) receptor.~~

~~50.——The method according to claim 49, wherein the targeting component is a PSMA receptor antibody or derivative of the PSMA receptor antibody.~~

~~51.——The method according to claim 50, wherein the targeting component is an antibody selected from the group consisting of J591, J415, J533, and E99.~~

~~52.——The method according to claim 47, wherein the cancer is breast cancer.~~

~~53.——The method according to claim 52, wherein the targeting component targets an HER-receptor family member.~~

~~54.——The method according to claim 53, wherein the targeting component is monoclonal antibody 4D5.~~

~~55.——The method according to claim 47, wherein the cancer is a blood cancer of B-cell lineage.~~

~~56.——The method according to claim 55, wherein the targeting component targets CD19.~~

~~57.——The method according to claim 56, wherein the targeting component is monoclonal antibody obexelimab or denintuzumab.~~

~~58. — The method according to claim 29, wherein said administering further comprises:~~

~~— administering uridine diphosphate galactose (UDP-gal), uridine diphosphate N-acetylgalactosamine (UDP-NAcGal), and/or guanosine diphosphate fucose (GDP-fucose).~~

~~59. — The method according to claim 49, wherein the targeting component targets PSMA receptor on tumor vascular endothelium.~~

~~60. — A pharmaceutical composition comprising:~~

~~—— the bi-functional therapeutic according to any of claims 1-28 and~~

~~—— a pharmaceutically acceptable carrier.~~

~~61. — A nucleic acid molecule encoding the bi-functional therapeutic according to any of claims 1-28.~~

~~62. — A nucleic acid construct comprising the nucleic acid molecule according to claim 61.~~

~~63. — A recombinant expression vector comprising the nucleic acid molecule according to claim 61.~~

~~64. — A recombinant host cell transformed with the nucleic acid molecule according to claim 61.~~

~~65.~~22. A bi-functional therapeutic for treating cancer comprising:

a targeting component which targets the prostate-specific membrane antigen (PSMA)/Folate hydrolase 1 (FOLH1) receptor and

a glycosyltransferase or active portion thereof which, when delivered to a tumor by said targeting component, enzymatically converts the tumor phenotype to that of an

incompatible allograft or xenograft, said glycosyltransferase or active portion thereof being coupled to said targeting component.

~~66~~23. The bi-functional therapeutic of claim ~~65~~22, wherein said targeting component comprises a heavy chain variable region, wherein said heavy chain variable region comprises:

a complementarity-determining region 1 (CDR-H1) comprising an amino acid sequence of SEQ ID NO: 10, or a modified amino acid sequence of SEQ ID NO: 10, said modified sequence having at least 80% sequence identity to SEQ ID NO: 10;

a complementarity-determining region 2 (CDR-H2) comprising an amino acid sequence of SEQ ID NO: 13, or a modified amino acid sequence of SEQ ID NO: 13, said modified sequence having at least 80% sequence identity to SEQ ID NO: 13; and

a complementarity-determining region 3 (CDR-H3) comprising an amino acid sequence of SEQ ID NO: 16, or a modified amino acid sequence of SEQ ID NO: 16, said modified sequence having at least 80% sequence identity to SEQ ID NO: 16; and

a light chain variable region, wherein said light chain variable region comprises:

a complementarity-determining region 1 (CDR-L1) having an amino acid sequence of SEQ ID NO: 19, or a modified amino acid sequence of SEQ ID NO: 19, said modified sequence having at least 80% sequence identity to SEQ ID NO: 19;

a complementarity-determining region 2 (CDR-L2) having an amino acid sequence of SEQ ID NO: 22, or a modified amino acid sequence of SEQ ID NO: 22, said modified sequence having at least 80% sequence identity to SEQ ID NO: 22; and

a complementarity-determining region 3 (CDR-L3) having an amino acid sequence of SEQ ID NO: 25, or a modified amino acid sequence of SEQ ID NO: 25, said modified sequence having at least 80% sequence identity to SEQ ID NO: 25.

~~67~~24. The bi-functional therapeutic of claim ~~65~~23, wherein said targeting component comprises a heavy chain variable region comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 28.

~~68. The bi-functional therapeutic of claims 66 or 67, wherein said targeting component further comprises a light chain variable region, wherein said light chain variable region comprises:~~

~~a complementarity determining region 1 (CDR L1) having an amino acid sequence of SEQ ID NO: 19, or a modified amino acid sequence of SEQ ID NO: 19, said modified sequence having at least 80% sequence identity to SEQ ID NO: 19;~~

~~a complementarity determining region 2 (CDR L2) having an amino acid sequence of SEQ ID NO: 22, or a modified amino acid sequence of SEQ ID NO: 22, said modified sequence having at least 80% sequence identity to SEQ ID NO: 22; and~~

~~a complementarity determining region 3 (CDR L3) having an amino acid sequence of SEQ ID NO: 25, or a modified amino acid sequence of SEQ ID NO: 25, said modified sequence having at least 80% sequence identity to SEQ ID NO: 25.~~

~~69.25.~~ The bi-functional therapeutic of claim ~~65~~23 or claim 24, wherein said targeting component comprises a light chain variable region comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 29.

~~70. The bi-functional therapeutic of claim 65, wherein said targeting component comprises a heavy chain variable region comprising the CDR H1 of SEQ ID NO: 10, the CDR H2 of SEQ ID NO: 13, and the CDR H3 of SEQ ID NO: 16, and a light chain variable region comprising the CDR L1 of SEQ ID NO: 19, the CDR L2 of SEQ ID NO: 22, and the CDR L3 of SEQ ID NO: 25.~~

~~71.26.~~ The bi-functional therapeutic of claim ~~65~~22, wherein said targeting component comprises a heavy chain variable region comprising ~~an~~the amino acid sequence ~~that is at least 80% identical to~~of SEQ ID NO: 28 and a light chain variable region comprising ~~an~~the amino acid sequence ~~that is at least 80% identical to~~of SEQ ID NO: 29.

~~72. The bi-functional therapeutic of claim 65, wherein said targeting component further comprises a signaling peptide, optionally wherein the signaling peptide has the sequence of amino acids 1-19 of SEQ ID NO: 34.~~

~~73.27.~~ The bi-functional therapeutic of any one of claims 65-22-26, wherein the glycosyltransferase or active portion thereof is selected from the group consisting of glycosyltransferase A (Alpha 1-3-N-Acetylgalactosaminyltransferase), ~~and glycosyltransferase B (alpha 1-3-galactosyltransferase),~~ alpha-gal-transferase, glycosyltransferase A (Gly268Ala), fucosyltransferase, and active portions thereof.

~~74. — The bi-functional therapeutic of claim 65, wherein the bi-functional therapeutic comprises:~~

- ~~(i) a first protein comprising the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35 and a second protein comprising the amino acid sequence of SEQ ID NO: 36;~~
- ~~(ii) a first protein comprising the amino acid sequence of SEQ ID NO: 37 or SEQ ID NO: 38 and a second protein comprising the amino acid sequence of SEQ ID NO: 39;~~
- ~~(iii) a first protein comprising the amino acid sequence of SEQ ID NO: 40 or SEQ ID NO: 41 and a second protein comprising the amino acid sequence of SEQ ID NO: 42;~~
- ~~(iv) a first protein comprising the amino acid sequence of SEQ ID NO: 43 or SEQ ID NO: 44 and a second protein comprising the amino acid sequence of SEQ ID NO: 45;~~
- ~~(v) the amino acid sequence of SEQ ID NO: 46;~~
- ~~(vi) the amino acid sequence of SEQ ID NO: 47;~~
- ~~(vii) the amino acid sequence of SEQ ID NO: 48; or~~
- ~~(viii) the amino acid sequence of SEQ ID NO: 49.~~

~~75. — A bi-functional therapeutic for treating cancer comprising:
a targeting component which targets a human epidermal growth factor receptor (HER) family member and
a glycosyltransferase which, when delivered to a tumor by said targeting component, enzymatically converts the tumor phenotype to that of an incompatible allograft or xenograft, said glycosyltransferase being coupled to said targeting component.~~

~~76. The bi-functional therapeutic of claim 75, wherein said targeting component comprises a heavy chain variable region, wherein said heavy chain variable region comprises:~~

~~————— a complementarity determining region 1 (CDR H1) comprising an amino acid sequence of SEQ ID NO: 11, or a modified amino acid sequence of SEQ ID NO: 11, said modified sequence having at least 80% sequence identity to SEQ ID NO: 11;~~

~~————— a complementarity determining region 2 (CDR H2) comprising an amino acid sequence of SEQ ID NO: 14, or a modified amino acid sequence of SEQ ID NO: 14, said modified sequence having at least 80% sequence identity to SEQ ID NO: 14; and~~

~~a complementarity determining region 3 (CDR H3) comprising an amino acid sequence of SEQ ID NO: 17, or a modified amino acid sequence of SEQ ID NO: 17, said modified sequence having at least 80% sequence identity to SEQ ID NO: 17.~~

~~77. The bi-functional therapeutic of claim 75, wherein said targeting component comprises a heavy chain variable region comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 30.~~

~~78. The bi-functional therapeutic of claim 76 or claim 77, wherein said targeting component further comprises a light chain variable region, wherein said light chain variable region comprises:~~

~~a complementarity determining region 1 (CDR L1) having an amino acid sequence of SEQ ID NO: 20, or a modified amino acid sequence of SEQ ID NO: 20, said modified sequence having at least 80% sequence identity to SEQ ID NO: 20;~~

~~a complementarity determining region 2 (CDR L2) having an amino acid sequence of SEQ ID NO: 23, or a modified amino acid sequence of SEQ ID NO: 23, said modified sequence having at least 80% sequence identity to SEQ ID NO: 23; and~~

~~a complementarity determining region 3 (CDR L3) having an amino acid sequence of SEQ ID NO: 26, or a modified amino acid sequence of SEQ ID NO: 26, said modified sequence having at least 80% sequence identity to SEQ ID NO: 26.~~

~~79. — The bi-functional therapeutic of claim 75, wherein said targeting component comprises a light chain variable region comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 31.~~

~~80. — The bi-functional therapeutic of claim 75, wherein said targeting component comprises a heavy chain variable region comprising the CDR H1 of SEQ ID NO: 11, the CDR H2 of SEQ ID NO: 14, and the CDR H3 of SEQ ID NO: 17, and a light chain variable region comprising the CDR L1 of SEQ ID NO: 20, the CDR L2 of SEQ ID NO: 23, and the CDR L3 of SEQ ID NO: 26.~~

~~81. — The bi-functional therapeutic of claim 75, wherein said targeting component comprises a heavy chain variable region comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 30 and a light chain variable region comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 31.~~

~~82. — The bi-functional therapeutic of claim 75, wherein said targeting component further comprises a signaling peptide, optionally wherein the signaling peptide has the sequence of amino acids 1-19 of SEQ ID NO: 50.~~

~~83. — The bi-functional therapeutic of claim 75, wherein the glycosyltransferase is selected from the group consisting of glycosyltransferase A (Alpha 1-3-N-Acetylgalactosaminyltransferase) and glycosyltransferase B (alpha 1-3-galactosyltransferase).~~

~~84. — The bi-functional therapeutic of claim 75, wherein the bi-functional therapeutic comprises:~~

- ~~(i) a first protein comprising the amino acid sequence of SEQ ID NO: 50 or SEQ ID NO: 51 and a second protein comprising the amino acid sequence of SEQ ID NO: 52;~~
- ~~(ii) a first protein comprising the amino acid sequence of SEQ ID NO: 53 or SEQ ID NO: 54 and a second protein comprising the amino acid sequence of SEQ ID NO: 55;~~
- ~~(iii) a first protein comprising the amino acid sequence of SEQ ID NO: 56 or SEQ ID NO: 57 and a second protein comprising the amino acid sequence of SEQ ID NO: 58;~~

- ~~(iv) the amino acid sequence of SEQ ID NO: 59;~~
- ~~(v) the amino acid sequence of SEQ ID NO: 60;~~
- ~~(vi) the amino acid sequence of SEQ ID NO: 61; or~~
- ~~(vii) the amino acid sequence of SEQ ID NO: 62.~~

~~85. — A bi-functional therapeutic for treating cancer comprising:
a targeting component which targets CD19 and
a glycosyltransferase which, when delivered to a tumor by said targeting
component, enzymatically converts the tumor phenotype to that of an incompatible allograft or
xenograft, said glycosyltransferase being coupled to said targeting component.~~

~~86. — The bi-functional therapeutic of claim 85, wherein said targeting
component comprises a heavy chain variable region, wherein said heavy chain variable region
comprises:~~

~~————— a complementarity determining region 1 (CDR H1) comprising an amino acid
sequence of SEQ ID NO: 12, or a modified amino acid sequence of SEQ ID NO: 12, said
modified sequence having at least 80% sequence identity to SEQ ID NO: 12;~~

~~————— a complementarity determining region 2 (CDR H2) comprising an amino acid
sequence of SEQ ID NO: 15, or a modified amino acid sequence of SEQ ID NO: 15, said
modified sequence having at least 80% sequence identity to SEQ ID NO: 15; and~~

~~————— a complementarity determining region 3 (CDR H3) comprising an amino acid
sequence of SEQ ID NO: 18, or a modified amino acid sequence of SEQ ID NO: 18, said
modified sequence having at least 80% sequence identity to SEQ ID NO: 18.~~

~~87. — The bi-functional therapeutic of claim 85, wherein said targeting
component comprises a heavy chain variable region comprising an amino acid sequence that is at
least 80% identical to SEQ ID NO: 32.~~

~~88. — The bi-functional therapeutic of claim 86 or claim 87, wherein said
targeting component further comprises a light chain variable region, wherein said light chain
variable region comprises:~~

a complementarity-determining region 1 (CDR-L1) having an amino acid sequence of SEQ ID NO: 21, or a modified amino acid sequence of SEQ ID NO: 21, said modified sequence having at least 80% sequence identity to SEQ ID NO: 21;

a complementarity-determining region 2 (CDR-L2) having an amino acid sequence of SEQ ID NO: 24, or a modified amino acid sequence of SEQ ID NO: 24, said modified sequence having at least 80% sequence identity to SEQ ID NO: 24; and

a complementarity-determining region 3 (CDR-L3) having an amino acid sequence of SEQ ID NO: 27, or a modified amino acid sequence of SEQ ID NO: 27, said modified sequence having at least 80% sequence identity to SEQ ID NO: 27.

89. — The bi-functional therapeutic of claim 85, wherein said targeting component comprises a light chain variable region comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 32.

90. — The bi-functional therapeutic of claim 85, wherein said targeting component comprises a heavy chain variable region comprising the CDR-H1 of SEQ ID NO: 12, the CDR-H2 of SEQ ID NO: 15, and the CDR-H3 of SEQ ID NO: 18, and a light chain variable region comprising the CDR-L1 of SEQ ID NO: 21, the CDR-L2 of SEQ ID NO: 24, and the CDR-L3 of SEQ ID NO: 27.

91. — The bi-functional therapeutic of claim 85, wherein said targeting component comprises a heavy chain variable region comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 32 and a light chain variable region comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 33.

92. — The bi-functional therapeutic of claim 85, wherein said targeting component further comprises a signaling peptide, optionally wherein the signaling peptide has the sequence of amino acids 1-19 of SEQ ID NO: 63.

93. — The bi-functional of claim 85, wherein the glycosyltransferase is selected from the group consisting of glycosyltransferase A (Alpha 1-3 N-

~~Acetylgalactosaminyltransferase), glycosyltransferase B (alpha 1-3-galactosyltransferase), and Marmoset α 1,3-galactosyltransferase.~~

~~94. The bi-functional therapeutic of claim 85, wherein the bi-functional therapeutic comprises the amino acid sequence of SEQ ID NO: 63.~~

28. A pharmaceutical composition comprising:
the bi-functional therapeutic according to any of claims 1-27 and
a pharmaceutically acceptable carrier.

29. A nucleic acid molecule encoding the bi-functional therapeutic according to any of claims 1-27.

30. A nucleic acid construct comprising the nucleic acid molecule according to claim 29.

31. A recombinant expression vector comprising the nucleic acid molecule according to claim 29.

32. A recombinant host cell transformed with the nucleic acid molecule according to claim 29, the nucleic acid construct according to claim 30, or the recombinant expression vector according to claim 31.

~~Use of a bi-functional therapeutic according to any one of claims 1-27 in the preparation of a medicament to treat cancer, where the bi-functional therapeutic is to be A method of treating cancer, said method comprising:~~

33. administering to a subject with cancer the bi-functional therapeutic according to any one of claims 1-27 under conditions effective to treat the cancer.

34. The method use according to claim 33, wherein the subject is a human.

———~~The method~~use according to claim 33 or claim 34, wherein uridine diphosphate-galactose (UDP-gal), uridine diphosphate-N-acetylgalactosamine (UDP-NAcGal), and/or guanosine diphosphate-fucose (GDP-fucose) is also to be administered to the subjectsaid method further comprises:

35. ~~administering uridine diphosphate-galactose (UDP-gal), uridine diphosphate N-acetylgalactosamine (UDP-NAcGal), and/or guanosine diphosphate-fucose (GDP-fucose).~~

36. The ~~method~~use of any one of claims 33-35, wherein the cancer is selected from the group consisting of lung cancer, gastric cancer, colorectal cancer, breast cancer, prostate cancer, blood cancer, cervical cancer, endometrial cancer, ovarian cancer, bladder cancer, renal cancer, brain cancer, hepatic cancer, esophageal cancer, adrenal cancer, head and neck cancer, melanoma, and pancreatic cancer.