

CLAIMS

What is claimed is:

1. A method of transducing immune cells in a subject in need thereof, comprising:
 - a) administering a multispecific antibody to render immune cells in the subject more transducible; and
 - b) administering a vector, optionally a viral vector;wherein the method transduces the immune cells.
2. The method of claim 1, wherein the immune cells are T cells.
3. The method of claim 1, wherein the vector is a lentiviral vector.
4. The method of claim 2, wherein the multispecific antibody comprises a T-cell antigen-specific binding domain.
5. The method of claim 4, wherein the T-cell antigen is CD3, CD4, CD8, or TCR.
6. The method of claim 4, wherein the multispecific antibody comprises a second antigen-specific binding domain.
7. The method of claim 6, wherein the second antigen is CD19.
8. The method of claim 6, wherein the second antigen is CD19, EpCAM, Her2/neu, EGFR, CD66e, CD33, EphA2, or MCSP.
9. The method of claim 6, wherein the second antigen is CD19, EpCAM, CD20, CD123, BCMA, B7-H3, CDE, or PSMA.
10. The method of claim 6, wherein the second antigen is a myeloid cell or dendritic cell antigen.

11. The method of claim 10, wherein the second antigen is CD33, DC-SIGN, CD11b, CD11c, or CD18.
12. The method of claim 1, wherein the multispecific antibody is a bispecific antibody.
13. The method of claim 12, wherein the bispecific antibody is a bispecific T-cell engager (BiTE).
14. The method of claim 13, wherein the BiTE is a CD19 x CD3 BiTE.
15. The method of claim 14, wherein the CD19 x CD3 BiTE is blinatumomab.
16. The method of any one of claims 1 to 15, wherein the multispecific antibody activates the immune cells.
17. The method of claim 16, wherein the multispecific antibody increases activation of the immune cells compared to administration of a vehicle control.
18. The method of any one of claims 1 to 15, wherein the multispecific antibody increases the number of immune cells in a lymph node of the subject.
19. The method of any one of claims 1 to 15, wherein the multispecific antibody increases transduction of the immune cells compared to administration of the viral vector alone.
20. The method of any one of claims 1 to 15, wherein the multispecific antibody enhances *in vivo* transduction of the immune cells by the viral vector.
21. The method of claim 20, wherein the multispecific antibody reduces the effective concentration (EC₅₀) of the viral vector.

22. The method of any one of claims 1 to 15, wherein the method achieves the same level of transduction of immune cells as a method comprising administering a higher concentration of the viral vector without administering the multispecific antibody.
23. The method of claim 1, wherein step a) and/or step b) comprises subcutaneous administration.
24. The method of claim 1, wherein step a) and/or step b) comprises intralymphatic administration.
25. The method of claim 2, wherein the vector is a viral vector comprising a polynucleotide encoding a T cell receptor or chimeric antigen receptor.
26. The method of claim 25, wherein the chimeric antigen receptor is an anti-CD19 chimeric antigen receptor.
27. The method of claim 2, wherein the vector is a viral vector comprising a polynucleotide encoding a cytokine receptor.
28. The method of claim 27, wherein the cytokine receptor is a drug-inducible cytokine receptor.
29. The method of claim 25, wherein the vector further comprises one or more transgenes.
30. The method of claim 29, wherein the viral vector comprises the transgene encoding a TGF β dominant negative receptor.
31. The method of claims 3, wherein the lentiviral vector comprises one or more cell surface receptors that bind to a ligand on a target host cell, heterologous viral envelope glycoproteins, fusion glycoproteins, T-cell activation or co-stimulation molecules, ligands for CD19 or a functional fragment thereof, cytokines or cytokine-based transduction

enhancers, and/or transmembrane proteins comprising a mitogenic domain and/or cytokine-based domain exposed on the surface and/or conjugated to the surface of the lentiviral vector.

32. The method of claim 31, wherein the one or more T-cell activation or co-stimulation molecules comprise one or more T-cell ligands.
33. The method of claim 31, wherein the lentiviral vector is pseudotyped with a Cocal virus envelop protein.
34. The method of claim 31, wherein the lentiviral vector is pseudotyped with a Nipah virus envelop protein.
35. The method of claim 34, wherein the Nipah envelop protein is engineered to bind EpCAM, CD4, or CD8.
36. The method of claims 1, wherein step a) or step b) comprises intravenous administration.
37. The method of claims 36, wherein both step a) and step b) comprise intravenous administration.
38. The method of claim 36 or 37, where the multispecific antibody is administered at a dose of about 0.001 mg/kg to about 1 mg/kg.
39. The method of claim 1, wherein the multispecific antibody binds specifically to CD3 and CD19, wherein the vector is a lentiviral vector pseudotyped with a Cocal virus envelop protein, and wherein the vector comprises a polynucleotide encoding an anti-CD19 chimeric antigen receptor and a transgene encoding a TGF β dominant negative receptor.
40. A method of transducing immune cells in a subject in need thereof, comprising:

a) administering a polynucleotide encoding a multispecific antibody to activate immune cells in the subject; and

b) administering a vector, optionally a viral vector;

wherein the method transduces the immune cells

41. The method of claim 40, wherein the polynucleotide encoding a multispecific antibody is an RNA.

42. The method of claim 40, wherein the immune cells are T cells.

43. The method of claim 40, wherein the vector is a lentiviral vector.

44. The method of claim 42, wherein the multispecific antibody comprises a T-cell antigen-specific binding domain.

45. The method of claim 44, wherein the T-cell antigen is CD3, CD4, CD8, or TCR.

46. The method of claim 44, wherein the multispecific antibody comprises a second antigen-specific binding domain.

47. The method of claim 46, wherein the second antigen is CD19.

48. The method of claim 46, wherein the second antigen is CD19, EpCAM, Her2/neu, EGFR, CD66e, CD33, EphA2, MCSP, CD22, CD79a, CD79b, or sIgM.

49. The method of claim 46, wherein the second antigen is CD19, EpCAM, CD20, CD123, BCMA, B7-H3, CDE, or PSMA.

50. The method of claim 46, wherein the second antigen is a lymph node antigen.

51. The method of claim 40, wherein the multispecific antibody is a trispecific antibody.

52. The method of claim 40, wherein the multispecific antibody is a bispecific antibody.
53. The method of claim 52, wherein the bispecific antibody is a bispecific T-cell engager (BiTE).
54. The method of claim 53, wherein the BiTE is a CD19 x CD3 BiTE.
55. The method of claim 54, wherein the CD19 x CD3 BiTE is blinatumomab.
56. The method of any one of claims 40-55, wherein the multispecific antibody activates the immune cells.
57. The method of any one of claims 40-55, wherein the multispecific antibody increases activation of the immune cells compared to administration of a vehicle control.
58. The method of any one of claims 40-55, wherein the multispecific antibody increases the number of immune cells in a lymph node of the subject.
59. The method of any one of claims 40-55, wherein the multispecific antibody increases transduction of the immune cells compared to administration of the viral vector alone.
60. The method of any one of claims 40-55, wherein the multispecific antibody enhances *in vivo* transduction of the immune cells by the viral vector.
61. The method of claim 60, wherein the multispecific antibody reduces the effective concentration (EC₅₀) of the viral vector.
62. The method of claim 60, wherein the method achieves the same level of transduction of immune cells as a method comprising administering a higher concentration of the viral vector without administering the multispecific antibody.

63. The method of claim 40, wherein step a) and/or step b) comprises subcutaneous administration.
64. The method of claim 40, wherein step a) and/or step b) comprises intralymphatic administration.
65. The method of claim 40, wherein step a) and/or step b) comprises intravenous administration.
66. The method of claim 40, wherein the viral vector comprises a polynucleotide encoding a T cell receptor or chimeric antigen receptor.
67. The method of claim 66, wherein the chimeric antigen receptor is an anti-CD19 chimeric antigen receptor.
68. The method of claim 40, wherein the viral vector comprises a polynucleotide encoding a cytokine receptor.
69. The method of claim 68, wherein the cytokine receptor is a drug-inducible cytokine receptor.
70. The method of claim 43, wherein the lentiviral vector comprises one or more cell surface receptors that bind to a ligand on a target host cell, heterologous viral envelope glycoproteins, fusion glycoproteins, T-cell activation or co-stimulation molecules, ligands for CD19 or a functional fragment thereof, cytokines or cytokine-based transduction enhancers, and/or transmembrane proteins comprising a mitogenic domain and/or cytokine-based domain exposed on the surface and/or conjugated to the surface of the lentiviral vector.

71. The method of claim 70, wherein one or more T-cell activation or co-stimulation molecules comprise one or more T-cell ligands.
72. The method of claim 40, wherein the vector further comprises one or more transgenes.
73. The method of claim 72, wherein the viral vector comprises the transgene encoding a TGF β dominant negative receptor.
74. The method of claim 43, wherein the lentiviral vector is pseudotyped with a Cocal virus envelop protein.
75. The method of claim 43, wherein the lentiviral vector is pseudotyped with a Nipah virus envelop protein.
76. The method of claim 75, wherein the Nipah envelop protein is engineered to bind EpCAM, CD4, or CD8.
77. The method of claim 43, wherein the multispecific antibody binds specifically to CD3 and CD19, wherein the vector is a lentiviral vector pseudotyped with a Cocal virus envelop protein, and wherein the vector comprises a polynucleotide encoding an anti-CD19 chimeric antigen receptor and a transgene encoding a TGF β dominant negative receptor.
78. A combination therapy for use in transducing immune cells *in vivo*, comprising a multispecific antibody and a vector, optionally a viral vector.
79. A pharmaceutical composition, comprising a multispecific antibody and a vector, optionally a viral vector.
80. A kit comprising 1) a multispecific antibody and 2) a vector, optionally a viral vector.

81. A kit comprising 1) a polynucleotide encoding a multispecific antibody and 2) a vector, optionally a viral vector.
82. The kit of claim 80 or 81, for use in:
- a) transducing immune cells in a subject in need thereof; and/or
 - b) treating a disease or disorder in a subject in need thereof.
83. A method of treating a disease or disorder in a subject in need thereof, comprising:
- a) administering a multispecific antibody to activate immune cells in the subject; and
 - b) before, after and concurrently with step a), administering a vector, optionally a viral vector.
84. The method of claim 83, wherein the method transduces the immune cells.
85. The method of claim 83 or 84, wherein the disease or disorder is a cancer.
86. The method of claim 83 or 84, wherein the disease or disorder is a hematological malignancy.
87. The method of claim 86, wherein the hematological malignancy is B cell lymphoma.
88. The method of claim 85, wherein the method treats the disease or disorder faster than administering the multispecific antibody alone and/or the vector alone.
89. The method of claim 85, wherein the method results in a better treatment outcome of the disease or disorder than administering the multispecific antibody alone and/or the vector alone.
90. The method of claim 85, wherein the multispecific antibody binds specifically to CD3 and CD19, wherein the vector is a lentiviral vector pseudotyped with a Cocal virus envelop

protein, and wherein the vector comprises a polynucleotide encoding an anti-CD19 chimeric antigen receptor and a transgene encoding a TGF β dominant negative receptor.

91. The method of claim 87, wherein the method results in faster depletion of malignant B cells in the subject than administering the multispecific antibody alone and/or the vector alone.
92. The method of claim 87, wherein the method results in lower number of residual malignant B cells and/or lower recurrence rate of the B cell lymphoma in the subject than administering the multispecific antibody alone and/or the vector alone.