

CLAIMS

What is claimed is:

1. A composition comprising a first therapeutic agent, wherein the therapeutic agent comprises:
 - (a) a first binding domain, wherein the first binding domain is a first antibody or functional fragment thereof that specifically interacts with an antigen on a target cell, and
 - (b) a second binding domain, wherein the second binding domain is a second antibody or functional fragment thereof that specifically interacts with a myeloid cell;wherein,
 - (i) the first therapeutic agent is coupled to a first component, wherein the first component is an additional therapeutic agent or a third binding domain, or
 - (ii) the composition comprises an additional therapeutic agent.
2. A composition comprising a therapeutic agent, wherein the therapeutic agent comprises: (a) a first binding domain that specifically interacts with an antigen of a target cell, (b) a second binding domain that specifically interacts with a myeloid cell, and (c) a third binding domain that specifically interacts with the myeloid cell.
3. The composition of claim 1 or 2, wherein the myeloid cell is a monocyte cell or a macrophage cell.
4. The composition of any one of claims 1-3, wherein the second binding domain that specifically interacts with a myeloid cell interacts with a phagocytic or tethering receptor of the myeloid cell.
5. The composition of claim 2, wherein the third binding domain that specifically interacts with a myeloid cell interacts with an extracellular region of a first phagocytic or tethering receptor of the myeloid cell.
6. The composition of any one of claims 1-5, wherein any one of binding domains of the therapeutic agent comprises the binding domain of a an antibody, a functional fragment of an antibody, a variable domain thereof, a V_H domain, a V_L domain, a VNAR domain, a V_{HH} domain, a single chain variable fragment (scFv), an Fab, a single-domain antibody (sdAb), a nanobody, a bispecific antibody, a diabody, or a functional fragment or a combination thereof.
7. The composition of any one of claims 1-6, wherein the antigen on the target cell to which the first binding domain binds, is a cancer antigen or a pathogenic antigen on the target cell or an autoimmune antigen.
8. The composition of any one of claims 1-7, wherein the antigen on the target cell to which the first binding domain binds, is a viral antigen.
9. The composition of any one of claims 1-8, wherein the antigen on the target cell to which the first

binding domain binds is a T-lymphocyte antigen.

10. The composition of any one of claims 1-9, wherein the antigen on the target cell to which the first binding domain binds is an extracellular antigen.
11. The composition of any one of claims 1-9, wherein the antigen on the target cell to which the first binding domain binds is an intracellular antigen.
12. The composition of any one of claims 1-11, wherein the antigen on the target cell to which the first binding domain binds is selected from the group consisting of Thymidine Kinase (TK1), Hypoxanthine-Guanine Phosphoribosyltransferase (HPRT), Receptor Tyrosine Kinase-Like Orphan Receptor 1 (ROR1), Mucin-1, Mucin-16 (MUC16), MUC1, Epidermal Growth Factor Receptor vIII (EGFRvIII), Mesothelin, Human Epidermal Growth Factor Receptor 2 (HER2), Mesothelin, EBNA-1, LEMD1, Phosphatidyl Serine, Carcinoembryonic Antigen (CEA), B-Cell Maturation Antigen (BCMA), Glypican 3 (GPC3), Follicular Stimulating Hormone receptor, Fibroblast Activation Protein (FAP), Erythropoietin-Producing Hepatocellular Carcinoma A2 (EphA2), EphB2, a Natural Killer Group 2D (NKG2D) ligand, Disialoganglioside 2 (GD2), CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD24, CD30, CD33, CD38, CD44v6, CD45, CD56CD79b, CD97, CD117, CD123, CD133, CD138, CD171, CD179a, CD213A2, CD248, CD276, PSCA, CS-1, CLECL1, GD3, PSMA, FLT3, TAG72, EPCAM, IL-1, an integrin receptor, PRSS21, VEGFR2, PDGFR-beta, SSEA-4, EGFR, NCAM, prostase, PAP, ELF2M, GM3, TEM7R, CLDN6, TSHR, GPRC5D, ALK, IGLL1 and combinations thereof.
13. The composition of any one of claims 1-12, wherein the antigen on the target cell to which the first binding domain binds is selected from the group consisting of CD2, CD3, CD4, CD5, CD7, CCR4, CD8, CD30, CD45, and CD56.
14. The composition of any one of claims 12 or 13, wherein the antigen on the target cell to which the first binding domain binds is an ovarian cancer antigen or a T lymphoma antigen.
15. The composition of any one of preceding claims, wherein the antigen on the target cell to which the first binding domain binds is an integrin receptor.
16. The composition of claim 1 or 2, wherein the second binding domain or the third binding domain binds to an integrin receptor.
17. The composition of claim 16, wherein the second binding domain or the third binding domain binds to an integrin receptor selected from the group consisting of $\alpha 1$, $\alpha 2$, αIIb , $\alpha 3$, $\alpha 4$, $\alpha 5$, $\alpha 6$, $\alpha 7$, $\alpha 8$, $\alpha 9$, $\alpha 10$, $\alpha 11$, αD , αE , αL , αM , αV , αX , $\beta 1$, $\beta 2$, $\beta 3$, $\beta 4$, $\beta 5$, $\beta 6$, $\beta 7$, and $\beta 8$.
18. The composition of any one of the preceding claims, wherein the therapeutic agent binds to a phagocytic or tethering receptor that comprises a phagocytosis activation domain.
19. The composition of claim 18, wherein the therapeutic agent binds to a receptor or a protein selected from the group consisting of the receptors listed in Table 2A and Table 2B, or a fragment

thereof.

20. The composition of claim 18, wherein the therapeutic agent binds to a phagocytic receptor selected from the group consisting of lectin, dectin 1, CD206, scavenger receptor A1 (SRA1), MARCO, CD36, CD163, MSR1, SCARA3, COLEC12, SCARA5, SCARB1, SCARB2, CD68, OLR1, SCARF1, SCARF2, CXCL16, STAB1, STAB2, SRCRB4D, SSC5D, CD205, CD207, CD209, RAGE, CD14, CD64, F4/80, CCR2, CX3CR1, CSF1R, Tie2, HuCR1g(L), CD64, CD32a, CD16a, CD89, Fc-alpha receptor I, CR1, CD35, CR3, CR4, Tim-1, Tim-4 and CD169.
21. The composition of any one of claims 1-20, wherein the therapeutic agent binds to a receptor comprising an intracellular signaling domain that comprises a pro-inflammatory signaling domain.
22. The composition of any one of claims 1-21, wherein the first therapeutic agent comprises a polypeptide that is less than 1000 amino acids or 1000 nm in length.
23. The composition of any one of claims 1-22, wherein the first therapeutic agent comprises a polypeptide that is less than 500 amino acids or 500 nm in length.
24. The composition of any one of claims 1-23, wherein the first therapeutic agent comprises a polypeptide that is 200-1000 amino acids or 200-1000 nm in length.
25. The composition of any one of claims 1-24, wherein engagement of the binding domains of the first therapeutic agent contacts the cancer cell to the myeloid cell.
26. The composition of claim 1, wherein the second binding domain specifically interacts with a myeloid cell and promotes phagocytosis activity of the myeloid cell.
27. The composition of claim 1, wherein the second binding domain specifically interacts with a myeloid cell and promotes inflammatory signaling of the myeloid cell.
28. The composition of claim 1, wherein the second binding domain specifically interacts with a myeloid cell or an adhesion molecule and promotes adhesion of the myeloid cell to the target cell.
29. The composition of claim 1, wherein the second binding domain specifically interacts with a myeloid cell and inhibits anti-phagocytic activity of the myeloid cell mediated by the target cell.
30. The composition of claim 1, wherein the second binding domain specifically interacts with a myeloid cell and inhibits anti-inflammatory activity of the myeloid cell mediated by the target cell.
31. The composition of claim 2, wherein the second and/or the third binding domain promotes phagocytic activity of the myeloid cell.
32. The composition of claim 2, wherein the second and/or the third binding domain promotes inflammatory signaling of the myeloid cell.

33. The composition of claim 2, wherein the second and/or the third binding domain specifically interacts with a myeloid cell or an adhesion molecule and promotes adhesion of the myeloid cell to the target cell.
34. The composition of claim 2, wherein the second and/or the third binding domain inhibits anti-phagocytic activity of the myeloid cell mediated by the target cell.
35. The composition of claim 2, wherein the second and/or the third binding domain inhibits anti-inflammatory activity of the myeloid cell mediated by the target cell.
36. The composition of any one of the preceding claims, wherein the therapeutic agent comprises a therapeutic polypeptide.
37. The composition of any one of the preceding claims, wherein the therapeutic agent comprises a recombinant nucleic acid encoding the therapeutic polypeptide.
38. The composition of claim 1, wherein the third binding domain or the additional therapeutic agent comprises a CD47 antagonist, a CD47 blocker, an antibody, a chimeric CD47 receptor, a sialidase, a cytokine, a proinflammatory gene, a procaspase, or an anti-cancer agent.
39. The composition of any one of the preceding claims, wherein the first binding domain, the second binding domain and the third binding domain bind to distinct non-identical target antigens.
40. The composition of claim 1 or 2, wherein the first binding domain, the second binding domain or the third binding domain is a ligand binding domain.
41. The composition of any one of the preceding claims, wherein the first, the second or the third binding domains are operably linked by one or more linkers.
42. The composition of claim 41, wherein the linker is a polypeptide.
43. The composition of claim 42, wherein the linker is a functional peptide.
44. The composition of claim 43, wherein the linker is a ligand for a receptor.
45. The composition of claim 44, wherein the linker is a ligand for a monocyte or macrophage receptor.
46. The composition of claim 43 or 44, wherein the linker activates the receptor.
47. The composition of claim 43 or 44, wherein the linker inhibits the receptor.
48. The composition of claim 44, wherein the linker is a ligand for a M2 macrophage receptor.
49. The composition of claim 43 or 44, wherein the linker is a ligand for a TLR receptor, such as TLR4.
50. The composition of claim any of the claims 43, 44, 45, 46, 48 or 49, wherein the linker activates a TLR receptor.
51. The composition of any one of the preceding claims, wherein the first, the second and /or the third binding domains are associated with a mask that binds to the binding domain.
52. The composition of claim 51, wherein the mask is an inhibitor that inhibits the interaction of

binding domain to its target when the mask remains associated with the respective binding domain.

53. The composition of claim 52, wherein the mask is associated with the binding domain via a peptide linker.
54. The composition of claim 53, wherein the peptide linker comprises a cleavable moiety.
55. The composition of claim 53, wherein the cleavable moiety is cleaved by a protein or an enzyme selectively abundant in the site of the cancer or tumor.
56. The composition of any one of claims 1-55, wherein the third binding domain that specifically interacts with an extracellular region of a second receptor of the macrophage activates the macrophage.
57. The composition of any one of claims 1-56, wherein upon binding of the therapeutic agent to the myeloid cell, the killing or phagocytosis activity of the myeloid cell is increased by at least 10%, or 20%, or 30%, or 40 %, or 50%, or 60%, or 70% or 90% or 100% compared to a myeloid cell not bound by the therapeutic agent, as measured by a particle uptake assay.
58. The composition of any one of claims 1-57, wherein engagement of the binding domains of first therapeutic agent triggers phagocytosis of the cancer cell by the myeloid cell.
59. The composition of any one of claims 1-58, wherein engagement of the additional therapeutic agent potentiates or increases the phagocytic killing of the cancer cell by the myeloid cell.
60. The composition of any one of claims 1-59, wherein the second or third binding domain binds to an extracellular of IgA, IgD, IgE, IgG, IgM, FcγRI, FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIA, FcγRIIB, FcRn, TRIM21, FcRL5.
61. The composition of any one of claims 1-60, wherein the second or the third binding domain comprises an M2 domain.
62. The composition of any one of claims 1-61, wherein the second or the third binding domain comprises a LIGHT domain.
63. The composition of any one of claims 1-62, wherein the second or the third binding domain comprises a HVEM domain.
64. The composition of any one of claims 1-63, wherein the second or the third binding domain comprises a GITR domain.
65. A pharmaceutical composition comprising:
 - a first therapeutic agent, wherein the therapeutic agent comprises one or more polypeptides or recombinant nucleic acids encoding the one or more polypeptides, wherein the one or more polypeptides comprise:
 - (a) a first binding domain, wherein the first binding domain is a first antibody or functional fragment thereof that specifically interacts with an antigen of a target cell, and

- (b) a second binding domain, wherein the second binding domain is a second antibody or functional fragment thereof that specifically interacts with a myeloid cell;
wherein,
(i) the first therapeutic agent is coupled to a first component, wherein the first component is an additional therapeutic agent or a third binding domain, or
(ii) the composition comprises an additional therapeutic agent; and
an acceptable pharmaceutical salt or excipient.
66. The pharmaceutical composition of claim 65, wherein the first therapeutic agent comprises a single polypeptide.
67. The pharmaceutical composition of claim 65, wherein the first therapeutic agent comprises multiple polypeptides.
68. The pharmaceutical composition of claim 65, wherein the first therapeutic agent is a recombinant nucleic acid encoding the one or more polypeptides.
69. The pharmaceutical composition of claim 65, further comprising a second therapeutic agent.
70. A method of treating a disease or condition in a subject in need thereof, comprising:
administering to the subject a pharmaceutical composition, comprising:
a first therapeutic agent, wherein the therapeutic agent comprises one or more polypeptides or recombinant nucleic acids encoding the one or more polypeptides, wherein the one or more polypeptides comprise:
(a) a first binding domain, wherein the first binding domain is a first antibody or functional fragment thereof that specifically interacts with an antigen of a target cell, and
(b) a second binding domain, wherein the second binding domain is a second antibody or functional fragment thereof that specifically interacts with a myeloid cell;
wherein,
(i) the first therapeutic agent is coupled to a first component, wherein the first component is an additional therapeutic agent or a third binding domain, or
(ii) the composition comprises an additional therapeutic agent; and
an acceptable pharmaceutical salt or excipient.
71. The method of claim 70, further comprising, administering a second therapeutic agent.
72. The method of claim 70, wherein the administering the pharmaceutical composition comprises administering the pharmaceutical composition intravenously.
73. The method of claim 70, wherein the administering the pharmaceutical composition comprises administering the pharmaceutical composition subcutaneously.
74. The method of claim 70, wherein the administering the pharmaceutical composition comprises injecting the pharmaceutical composition.

75. The composition of claim 1 or 2, wherein the first binding domain comprises a sequence having an amino acid sequence with at least 80%, 85%, 90%, 95% or 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 27, 28, 111, 112, 113, 115, 143 and 144.
76. The composition of claim 1 or 2, wherein the second binding domain comprises a sequence having an amino acid sequence with at least 80%, 85%, 90%, 95% or 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 141 and 142.
77. The composition of claim 1, wherein the first component comprises an amino acid sequence GGQEINSSYGG (SEQ ID NO: 105) or QEINSSY (SEQ ID NO: 129).
78. The composition of claim 1, wherein the first component comprises an amino acid sequence GGAPPHALSGG (SEQ ID NO: 109) or APPHALS (SEQ ID NO: 137).
79. The composition of claim 49 or 50, wherein the linker comprises an amino acid sequence GGQEINSSYGG (SEQ ID NO: 105), or QEINSSY (SEQ ID NO: 129) or GGAPPHALSGG (SEQ ID NO: 109) or APPHALS (SEQ ID NO: 137).
80. A bispecific or trispecific engager, comprising a sequence having an amino acid sequence with at least 80%, 85%, 90%, 95% or 100% sequence identity to SEQ ID NO: 151.
81. A bispecific or trispecific engager, comprising a sequence having an amino acid sequence with at least 80%, 85%, 90%, 95% or 100% sequence identity to SEQ ID NO: 152.