

Claims

1. A polypeptide construct comprising a nucleotide binding domain (NBD) amino acid (aa) sequence, and tumor-specific binder (TSB) aa sequence, optionally joined by a linker peptide sequence; wherein the NBD comprises one or more adenosine triphosphate (ATP) binding sites and can either homodimerize or heterodimerize with a cognate non-identical NBD in the presence of ATP (e.g., the NBD of TAP1 or TAP2 which can heterodimerize).
2. The polypeptide construct of claim 1, further comprising a scaffold aa sequence.
3. A composition comprising a first polypeptide construct and a second polypeptide construct of claim 2, wherein the first polypeptide construct comprises a first NBD aa sequence and the second polypeptide construct comprises a second NBD aa sequence, and the first and the second NBD aa sequences are cognate sequences that may homodimerize or heterodimerize in the presence of ATP to form a heterodimer complex.
4. The composition of claim 3, wherein the first and second polypeptide constructs homodimerize.
5. The composition of claim 4, wherein the TSB of the first polypeptide construct and the TSB of the second polypeptide construct recognize (bind to) a single tumor-associated antigen (TAA) from the group consisting of: mesothelin, Epithelial Cell Adhesion Molecule (EpCAM), Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4), carbonic anhydrase IX (CAIX), cadherins, carcinoembryonic antigen (CEA), cellular- mesenchymal epithelial transition factor (c-MET), Epidermal Growth Factor Receptor (EGFR) family members, Ephrin Type-A Receptor 3 (EphA3), Fibroblast Activation Protein Alpha (FAP), folate-binding protein, Folate Receptor alpha (FR-alpha), Erb-B2 Receptor Tyrosine Kinase 2 (HER2), Erb-B2 Receptor Tyrosine Kinase 3 (HER3), Insulin Like Growth Factor 1 Receptor (IGF-1R), integrin $\alpha\text{V}\beta\text{3}$, integrin $\alpha\text{5}\beta\text{1}$, Solute Carrier Family 39 Member 6 (Liv1), a Melanoma-Associated Antigen family A member (MAGEA), a Melanoma-Associated Antigen family C member (MAGEC), a mucin (e.g., MUC1), a New York Esophageal Squamous Cell Carcinoma 1 protein (NY-ESO-1, Cancer/Testis Antigen 1A, Cancer/Testis Antigen 1B), Cancer/Testis Antigen 2 (NY-ESO-2, CTAG2), Prostate-Specific Membrane Antigen (PSMA), Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL), Receptor Tyrosine Kinase Like Orphan Receptor 1 (ROR1), tenascin, TNF Receptor Superfamily Member 10a (TRAILR1), TNF Receptor Superfamily Member 10b (TRAILR2), and Vascular Endothelial Growth Factor Receptor (VEGFR).
6. The composition of claim 5, wherein each scaffold comprises an immunoglobulin polypeptide sequence.
7. The composition of claim 6, wherein each scaffold comprises an IgFc aa sequence.

8. The composition of claim 7, wherein each scaffold comprises an independently selected non-dimerizing IgFc.
9. The composition of claim 8, wherein the immunoglobulin Fc (IgFc) polypeptide aa sequence may induce antibody related effector functions or the IgFc polypeptide aa sequence comprises one or more substitutions that enhance at least one antibody related effector function selected from ADCC, ADCP, and CDC.
10. The composition of claim 9, wherein each NBD is a NBD of an ATP-binding cassette (ABC) transporter.
11. The composition of claim 10, wherein the NBD comprises a TAP1 NBD.
12. The composition of claim 11, wherein the TAP1 NBD comprises an aa sequence of any one of SEQ ID NOs:10, 87, or 88, or a sequence having greater than 90% or greater than 95% sequence identity to any one of those sequences.
13. A polypeptide construct comprising a nucleotide binding domain (NBD) amino acid (aa) sequence, and an activating domain (AD) aa sequence, optionally joined by a linker peptide sequence; wherein the NBD comprises one or more adenosine triphosphate (ATP) binding sites and can either homodimerize or heterodimerize with a cognate non-identical NBD in the presence of ATP.
14. The polypeptide construct of claim 13, further comprising a scaffold aa sequence.
15. The polypeptide construct of claim 13, wherein the AD is selected from:
 - (i) IL-7, IL-15, IL-12 or a subunit thereof;
 - (ii) an aa sequence that binds to one of PD1, CD40, 4-1BB, IL-10R, CTLA-4, or CD28.
16. A composition comprising a first polypeptide construct and a second polypeptide construct of any of claims 13-15, wherein:

the first polypeptide construct comprises a first NBD aa sequence and the second polypeptide construct comprises a second NBD aa sequence, and the first and second NBD aa sequences are cognate sequences that may heterodimerize; and

the first polypeptide construct comprises the p40 subunit of IL-12 and the second polypeptide construct comprises the p35 subunit of IL-12.
17. The composition of claim 16, wherein the first NBD comprises a TAP1 NBD aa sequence and the second NBD comprises a TAP2 NBD aa sequence.
18. A polypeptide construct comprising a nucleotide binding domain (NBD) amino acid (aa) sequence, and an immune cell engager (ICE) aa sequence, optionally joined by a linker peptide sequence; wherein the NBD comprises one or more adenosine triphosphate (ATP) binding sites and can

heterodimerize with a cognate non-identical NBD in the presence of ATP (e.g., the NBD of TAP1 or TAP2 which can heterodimerize).

19. The polypeptide construct of claim 18, further comprising a scaffold aa sequence.
20. A composition comprising a first polypeptide construct of claims 1 or 2, and a second polypeptide construct of claims 18 or 19, wherein:
 - (i) the first polypeptide construct comprises one or more first heterodimerizing NBD aa sequences and the second polypeptide construct comprises one or more second heterodimerizing NBD aa sequences;
 - (ii) each of the one or more first heterodimerizing NBD aa sequences are cognate binding partners of the one or more second heterodimerizing NBD aa sequences;
 - (iii) the first polypeptide construct and the second polypeptide construct bind to each other through interactions between at least one of the one or more first heterodimerizing NBD aa sequences and at least one of the one or more second heterodimerizing NBD sequences in the presence of ATP to form a heterodimer or higher order complex of the first and second polypeptide constructs;
 - (iv) the TSB of the first polypeptide construct binds to a tumor-associated antigen (TAA) from the group consisting of: mesothelin, Epithelial Cell Adhesion Molecule (EpCAM), Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4), carbonic anhydrase IX (CAIX), cadherins, carcinoembryonic antigen (CEA), cellular- mesenchymal epithelial transition factor (c-MET), Epidermal Growth Factor Receptor (EGFR) family members, Ephrin Type-A Receptor 3 (EphA3), Fibroblast Activation Protein Alpha (FAP), folate-binding protein, Folate Receptor alpha (FR-alpha), Erb-B2 Receptor Tyrosine Kinase 2 (HER2), Erb-B2 Receptor Tyrosine Kinase 3 (HER3), Insulin Like Growth Factor 1 Receptor (IGF-1R), integrin α V β 3, integrin α 5 β 1, Solute Carrier Family 39 Member 6 (Liv1), a Melanoma-Associated Antigen family A member (MAGEA), a Melanoma-Associated Antigen family C member (MAGEC), a mucin (e.g., MUC1), a New York Esophageal Squamous Cell Carcinoma 1 protein (NY-ESO-1, Cancer/Testis Antigen 1A, Cancer/Testis Antigen 1B), Cancer/Testis Antigen 2 (NY-ESO-2, CTAG2), Prostate-Specific Membrane Antigen (PSMA), Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL), Receptor Tyrosine Kinase Like Orphan Receptor 1 (ROR1), tenascin, TNF Receptor Superfamily Member 10a (TRAILR1), TNF Receptor Superfamily Member 10b (TRAILR2), and Vascular Endothelial Growth Factor Receptor (VEGFR); and
 - (v) the ICE of the second polypeptide construct comprises a Fab, Fab', scFv, aptamer, or nanobody with affinity for a protein selected from the group consisting of: CD3, CD4, CD8, α β TCR, CD2, TCR α chain, TCR β chain, δ γ TCR, TCR γ chain, TCR δ chain, TRGV9, CD84, CXCR1, CD13, CD33, CD34, and CD16.

21. A method of treating a cancer comprising administering a construct or composition of any one of aspects 1-20 to a patient or subject.
22. The use of a construct or composition of any of aspects 1-20 for the preparation of a medicament for the treatment of a cancer.
23. A polypeptide construct or composition of any of aspects 1-20 for the treatment of a cancer.
24. The method, use, construct or composition of claims 21-23, wherein the cancer comprises a solid tumor.
25. The method, use, construct or composition of claim 24, wherein the cancer is a mesothelioma, melanoma, sarcoma, carcinoma, carcinosarcoma, lymphoma, or a germ cell tumor.
26. A nucleic acid comprising a sequence encoding one or more constructs, or one or more constructs of a composition of any of aspects 1-20.
27. A vector comprising the nucleic acid of claim 26, optionally under the control of a promoter (e.g., a constitutive promoter) or an inducible promoter.
28. A cell comprising the vector or nucleic acid of claims 26 or 27.
29. The cell of claim 28, wherein the cell is a mammalian cell, yeast cell, insect cell, or bacterial cell.