[0006a] In one aspect, the present disclosure refers to a target-binding polypeptide comprising an amino acid sequence of

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALGGSEAELAX_{30}FEX_{33}X_{34}IAX_{37}FEX_{40}X_{41}LQ$
$X_{44}YKGKGNPEVEALRKEAAAIRDELQAYRHN$ (SEQ ID NO:2),

$MGSWAEFKQRLAAIKTRLEALGGSEAELAAFX_{32}X_{33}EIX_{36}AFX_{39}X_{40}ELX_{43}AYKGKGNPEVE$
$ALX_{57}X_{58}EAX_{61}AIX_{64}X_{65}ELX_{68}AYRHN$ (SEQ ID NO:3),

$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALGGSEAELAAFEKEIAAFESELQAYKGKGNPEVEX_5$
$_5LRX_{58}X_{59}AAX_{62}IRX_{65}X_{66}LQAYRHN$ (SEQ ID NO:4),

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALGGSEAELAAFX_{32}X_{33}EIX_{36}AFX_{39}X_{40}ELX_{43}AYKGK$
$GNPEVEX_{55}LRX_{58}X_{59}AAX_{62}IRX_{65}X_{66}LQAYRHN$ (SEQ ID NO:5),

$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALGGSEAELAX_{30}FEX_{33}X_{34}IAX_{37}FEX_{40}X_{41}LQ$
$X_{44}YKGKGNPEVEALX_{57}X_{58}EAX_{61}AIX_{64}X_{65}ELX_{68}AYRHN$ (SEQ ID NO:6),

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALZ_1EAELAX_{28}FEX_{31}X_{32}IAX_{35}FEX_{38}X_{39}LQX_{42}YZ_2NPE$
$VEALRKEAAAIRDELQAYRHN$ (SEQ ID NO:7),

$MGSWAEFKQRLAAIKTRLEALZ_1EAELAAFX_{30}X_{31}EIX_{34}AFX_{37}X_{38}ELX_{41}AYZ_2NPEVEALX_{52}$
$X_{53}EAX_{56}AIX_{59}X_{60}ELX_{63}AYRHN$ (SEQ ID NO:8),

$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALZ_1EAELAAFEKEIAAFESELQAYZ_2NPEVE$
$X_{50}LRX_{53}X_{54}AAX_{57}IRX_{60}X_{61}LQAYRHN$ (SEQ ID NO:9),

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALZ_1EAELAAFX_{30}X_{31}EIX_{34}AFX_{37}X_{38}ELX_{41}AYZ_2NPEV$
$EX_{50}LRX_{53}X_{54}AAX_{57}IRX_{60}X_{61}LQAYRHN$ (SEQ ID NO:10) or

$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALZ_1EAELAX_{28}FEX_{31}X_{32}IAX_{35}FEX_{38}X_{39}LQX_{42}Y$
$Z_2NPEVEALX_{52}X_{53}EAX_{56}AIX_{59}X_{60}ELX_{63}AYRHN$ (SEQ ID NO:11), wherein

(a) X_n is a natural or non-natural amino acid;

(b) Z_1 and Z_2 comprise between about 2 to about 30 natural or non-natural amino acids;

(c) the target-binding polypeptide specifically binds a target of interest, wherein the specific binding of the target-binding polypeptide to the target of interest is greater than the binding of a reference polypeptide comprising the amino acid sequence of SEQ ID NO:1 to the target of interest; and

(d) the target-binding polypeptide does not comprise the amino acid sequence of SEQ ID NO:50.

[0006c] In yet another aspect, the present disclosure refers to a fusion protein comprising a first and second target-binding polypeptide as disclosed herein wherein the first and second target-binding polypeptide exhibits binding specificity for a tumor target, optionally wherein the first and second target-binding polypeptide exhibits binding specificity for different tumor targets.

[0006d] In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising the target-binding polypeptide as disclosed herein, or the fusion protein as disclosed herein and further comprising a pharmaceutically acceptable carrier.

[0006e] In yet another aspect, the present disclosure refers to a kit comprising the target-binding polypeptide as disclosed herein, or the fusion protein as disclosed herein.

[0006f] In yet another aspect, the present disclosure refers to an isolated nucleic acid molecule encoding the target-binding polypeptide as disclosed herein, or the fusion protein as disclosed herein.

[0006g] In a further aspect, the present disclosure refers to a vector comprising the isolated nucleic acid molecule as disclosed herein, and optionally further comprising a nucleotide sequence which regulates the expression of the target-binding polypeptide, or fusion protein encoded by the nucleic acid molecule.

[0006h] In yet another aspect, the present disclosure refers to a host cell comprising the nucleic acid molecule as disclosed herein or the vector as disclosed herein.

[0006i] In yet another aspect, the present disclosure refers to a cell line engineered to express the target-binding polypeptide as disclosed herein, or the fusion protein as disclosed herein.

[0006j] In yet another aspect, the present disclosure refers to a chimeric antigen receptor (CAR), wherein the CAR comprises

(a) a targeting domain,

(b) a transmembrane domain, and

(c) an intracellular signaling domain,

wherein the targeting domain comprises the target-binding polypeptide as disclosed herein, or the fusion protein as disclosed herein.

[0006k] In yet another aspect, the present disclosure refers to an isolated nucleic acid molecule comprising a sequence encoding the CAR as disclosed herein.

[0006l] In yet another aspect, the present disclosure refers to a cell comprising a nucleic acid molecule comprising a sequence encoding the CAR as disclosed herein, optionally wherein the cell is a T cell or a natural killer (NK) cell, and optionally wherein the cell exhibits an anti-tumor immunity when the target-binding polypeptide, or fusion protein binds to its corresponding tumor antigen.

[0006m] In yet another aspect, the present disclosure refers to the use of an immune cell comprising the CAR as disclosed herein for the manufacture of a medicament for the treatment of cancer.

[0006n] In yet another aspect, the present disclosure refers to the use of an immune cell comprising a chimeric antigen receptor (CAR) for the manufacture of a medicament for the treatment of cancer, wherein the CAR comprises:

(a) a target binding domain comprising a target-binding polypeptide having an amino acid sequence selected from the group consisting of

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALGGSEAELAX_{30}FEX_{33}X_{34}IAX_{37}FEX_{40}X_{41}LQX_{44}YKGKGNPEVEALRKEAAAIRDELQAYRHN$ (SEQ ID NO:2),

$MGSWAEFKQRLAAIKTRLEALGGSEAELAAFX_{32}X_{33}EIX_{36}AFX_{39}X_{40}ELX_{43}AYKGKGNPEVEALX_{57}X_{58}EAX_{61}AIX_{64}X_{65}ELX_{68}AYRHN$ (SEQ ID NO:3),

$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALGGSEAELAAFEKEIAAFESELQAYKGKGNPEVEX_{55}LRX_{58}X_{59}AAX_{62}IRX_{65}X_{66}LQAYRHN$ (SEQ ID NO:4),

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALGGSEAELAAFX_{32}X_{33}EIX_{36}AFX_{39}X_{40}ELX_{43}AYKGKGNPEVEX_{55}LRX_{58}X_{59}AAX_{62}IRX_{65}X_{66}LQAYRHN$ (SEQ ID NO:5), and

$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALGGSEAELAX_{30}FEX_{33}X_{34}IAX_{37}FEX_{40}X_{41}LQX_{44}YKGKGNPEVEALX_{57}X_{58}EAX_{61}AIX_{64}X_{65}ELX_{68}AYRHN$ (SEQ ID NO:6), wherein X_n is a natural or non-natural amino acid, wherein X_n is not a cysteine or a proline residue, wherein the target-binding polypeptide specifically binds a target of interest expressed by a cancer cell, and wherein the specific binding of the target-binding polypeptide to the target of interest is greater than binding of a polypeptide according to SEQ ID NO:1 to the target of interest,

(b) a transmembrane domain selected from 41BB and CD28, and

(c) an intracellular domain, wherein the intracellular domain comprises a signaling domain selected from an alpha, beta, or zeta chain of the T cell receptor.

[0006o] In yet another aspect, the present disclosure refers to a method for transforming a reference polypeptide into a target-binding polypeptide capable of specifically binding to a target of interest, the method comprising:

(a) modifying a plurality of amino acid residues from the reference polypeptide to generate a plurality of candidate target-binding polypeptides; wherein the candidate target-binding polypeptides comprise a variant of the amino acid sequence of SEQ ID NO: 1, wherein the candidate target-binding polypeptides comprise three anti-parallel alpha helices joined by linker peptides, wherein the amino acid residues modified are solvent accessible or solvent inaccessible, and wherein the modification comprises one or more conservative or non-conservative amino acid substitutions and does not include a substitution with a cysteine or a proline;

(b) packaging the plurality of candidate target-binding polypeptides in a plurality of vectors to generate a candidate library; and

(c) screening the candidate library for candidate target-binding polypeptides that exhibit specific binding to the target of interest,

wherein the candidate target-binding polypeptides comprise an amino acid sequence selected from the group consisting of

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALGGSEAELAX_{30}FEX_{33}X_{34}IAX_{37}FEX_{40}X_{41}LQ$
$X_{44}YKGKGNPEVEALRKEAAAIRDELQAYRHN$ (SEQ ID NO:2),

$MGSWAEFKQRLAAIKTRLEALGGSEAELAAFX_{32}X_{33}EIX_{36}AFX_{39}X_{40}ELX_{43}AYKGKGNPEVE$
$ALX_{57}X_{58}EAX_{61}AIX_{64}X_{65}ELX_{68}AYRHN$ (SEQ ID NO:3),

$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALGGSEAELAAFEKEIAAFESELQAYKGKGNPEVEX_5$
$_5LRX_{58}X_{59}AAX_{62}IRX_{65}X_{66}LQAYRHN$ (SEQ ID NO:4),

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALGGSEAELAAFX_{32}X_{33}EIX_{36}AFX_{39}X_{40}ELX_{43}AYKGK$
$GNPEVEX_{55}LRX_{58}X_{59}AAX_{62}IRX_{65}X_{66}LQAYRHN$ (SEQ ID NO:5),

$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALGGSEAELAX_{30}FEX_{33}X_{34}IAX_{37}FEX_{40}X_{41}LQ$
$X_{44}YKGKGNPEVEALX_{57}X_{58}EAX_{61}AIX_{64}X_{65}ELX_{68}AYRHN$ (SEQ ID NO:6),

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALZ_1EAELAX_{28}FEX_{31}X_{32}IAX_{35}FEX_{38}X_{39}LQX_{42}YZ_2NPE$
$VEALRKEAAAIRDELQAYRHN$ (SEQ ID NO:7),

$MGSWAEFKQRLAAIKTRLEALZ_1EAELAAFX_{30}X_{31}EIX_{34}AFX_{37}X_{38}ELX_{41}AYZ_2NPEVEALX_{52}$

$X_{53}EAX_{56}AIX_{59}X_{60}ELX_{63}AYRHN$ (SEQ ID NO:8),

$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALZ_1EAELAAFEKEIAAFESELQAYZ_2NPEVE$

$X_{50}LRX_{53}X_{54}AAX_{57}IRX_{60}X_{61}LQAYRHN$ (SEQ ID NO:9),

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALZ_1EAELAAFX_{30}X_{31}EIX_{34}AFX_{37}X_{38}ELX_{41}AYZ_2NPEV$

$EX_{50}LRX_{53}X_{54}AAX_{57}IRX_{60}X_{61}LQAYRHN$ (SEQ ID NO:10) and

$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALZ_1EAELAX_{28}FEX_{31}X_{32}IAX_{35}FEX_{38}X_{39}LQX_{42}Y$

$Z_2NPEVEALX_{52}X_{53}EAX_{56}AIX_{59}X_{60}ELX_{63}AYRHN$ (SEQ ID NO:11), wherein X_n is a natural or non-natural amino acid and Z_1 and Z_2 comprise between about 2 to about 30 natural or non-natural amino acids.

[0006p] In yet another aspect, the present disclosure refers to virus-like particles (VLPs) comprising a fusion polypeptide comprising the target-binding polypeptide as disclosed herein, wherein the VLPs are suitable for use as immunogens for antibody generation, wherein said antibodies are directed against the target-binding polypeptide.

WHAT IS CLAIMED IS:

1. A target-binding polypeptide comprising an amino acid sequence of MGSWX_5X_6FKX_9X_{10}LAX_{13}IK$X_{16}X_{17}$LEALGGSEAELAX_{30}FE$X_{33}X_{34}$IAX_{37}FE$X_{40}X_{41}$LQX_{44}YKGKGNPEVEALRKEAAAIRDELQAYRHN (SEQ ID NO:2), MGSWAEFKQRLAAIKTRLEALGGSEAELAAF$X_{32}X_{33}$EIX_{36}AF$X_{39}X_{40}$ELX_{43}AYKGKGNPEVEAL$X_{57}X_{58}$EAX_{61}AI$X_{64}X_{65}$ELX_{68}AYRHN (SEQ ID NO:3), MGSWX_5EFX_8X_9RLX_{12}AI$X_{15}X_{16}$RLX_{19}ALGGSEAELAAFEKEIAAFESELQAYKGKGNPEVEX_{55}LR$X_{58}X_{59}$AAX_{62}IR$X_{65}X_{66}$LQAYRHN (SEQ ID NO:4), MGSWX_5X_6FKX_9X_{10}LAX_{13}IK$X_{16}X_{17}$LEALGGSEAELAAF$X_{32}X_{33}$EIX_{36}AF$X_{39}X_{40}$ELX_{43}AYKGKGNPEVEX_{55}LR$X_{58}X_{59}$AAX_{62}IR$X_{65}X_{66}$LQAYRHN (SEQ ID NO:5), MGSWX_5EFX_8X_9RLX_{12}AI$X_{15}X_{16}$RLX_{19}ALGGSEAELAX_{30}FE$X_{33}X_{34}$IAX_{37}FE$X_{40}X_{41}$LQX_{44}YKGKGNPEVEAL$X_{57}X_{58}$EAX_{61}AI$X_{64}X_{65}$ELX_{68}AYRHN (SEQ ID NO:6), MGSWX_5X_6FKX_9X_{10}LAX_{13}IK$X_{16}X_{17}$LEALZ$_1$EAELAX_{28}FE$X_{31}X_{32}$IAX_{35}FE$X_{38}X_{39}$LQX_{42}YZ$_2$NPEVEALRKEAAAIRDELQAYRHN (SEQ ID NO:7), MGSWAEFKQRLAAIKTRLEALZ$_1$EAELAAF$X_{30}X_{31}$EIX_{34}AF$X_{37}X_{38}$ELX_{41}AYZ$_2$NPEVEAL$X_{52}X_{53}$EAX_{56}AI$X_{59}X_{60}$ELX_{63}AYRHN (SEQ ID NO:8), MGSWX_5EFX_8X_9RLX_{12}AI$X_{15}X_{16}$RLX_{19}ALZ$_1$EAELAAFEKEIAAFESELQAYZ$_2$NPEVEX_{50}LR$X_{53}X_{54}$AAX_{57}IR$X_{60}X_{61}$LQAYRHN (SEQ ID NO:9), MGSWX_5X_6FKX_9X_{10}LAX_{13}IK$X_{16}X_{17}$LEALZ$_1$EAELAAF$X_{30}X_{31}$EIX_{34}AF$X_{37}X_{38}$ELX_{41}AYZ$_2$NPEVEX_{50}LR$X_{53}X_{54}$AAX_{57}IR$X_{60}X_{61}$LQAYRHN (SEQ ID NO:10) or MGSWX_5EFX_8X_9RLX_{12}AI$X_{15}X_{16}$RLX_{19}ALZ$_1$EAELAX_{28}FE$X_{31}X_{32}$IAX_{35}FE$X_{38}X_{39}$LQX_{42}YZ$_2$NPEVEAL$X_{52}X_{53}$EAX_{56}AI$X_{59}X_{60}$ELX_{63}AYRHN (SEQ ID NO:11), wherein

   (a) X_n is a natural or non-natural amino acid;

   (b) Z_1 and Z_2 comprise between about 2 to about 30 natural or non-natural amino acids;

   (c) the target-binding polypeptide specifically binds a target of interest, wherein the specific binding of the target-binding polypeptide to the target of interest is greater than the binding of a reference polypeptide comprising the amino acid sequence of SEQ ID NO:1 to the target of interest; and

   (d) the target-binding polypeptide does not comprise the amino acid sequence of SEQ ID NO:50.

2. The target-binding polypeptide of claim 1 comprising an amino acid sequence of SEQ ID NO: 4.

3. The target-binding polypeptide of claim 1 or claim 2, wherein X_n is not a cysteine or a proline.

4. The target-binding polypeptide of any one of claims 1 to 3, wherein the target of interest is a cancer antigen, optionally wherein the cancer antigen is PD-L1, CD137, or CD123, and optionally wherein
   (a) the target of interest is PD-L1 and the target-binding polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO: 43, and SEQ ID NO:44;
   (b) the target of interest is CD137 and the target-binding polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, and SEQ ID NO:19;
   (c) the target of interest is CD123 and the target-binding polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 92-126 and SEQ ID NO:127; or
   (d) the target of interest is CD123 and the target-binding polypeptide competes with the target-binding polypeptide of (c) for binding to CD123.

5. A fusion protein comprising a first and second target-binding polypeptide according to any one of claims 1 to 4 wherein the first and second target-binding polypeptide exhibits binding specificity for a tumor target, optionally wherein the first and second target-binding polypeptide exhibits binding specificity for different tumor targets.

6. The target-binding polypeptide of any one of claims 1 to 4, or the fusion protein of claim 5, wherein the target-binding polypeptide or fusion protein is labeled and optionally, wherein the label is a biotin moiety or is selected from the group consisting of an enzymatic label, a fluorescent label, a luminescent label, and a bioluminescent label.

7. The target-binding polypeptide of any one of claims 1 to 4 and 6, or the fusion protein of claim 5 or claim 6, wherein the target-binding polypeptide or fusion protein is conjugated to a therapeutic or cytotoxic agent.

8. A pharmaceutical composition comprising the target-binding polypeptide of any one of claims 1 to 4, 6 and 7, or the fusion protein of any one of claims 5 to 7 and further comprising a pharmaceutically acceptable carrier.

9. A kit comprising the target-binding polypeptide of any one of claims 1 to 4, 6 and 7, or the fusion protein of any one of claims 5 to 7.

10. An isolated nucleic acid molecule encoding the target-binding polypeptide of any one of claim 1 to 4, or the fusion protein of claim 5.

11. A vector comprising the isolated nucleic acid molecule of claim 10, and optionally further comprising a nucleotide sequence which regulates the expression of the target-binding polypeptide or fusion protein encoded by the nucleic acid molecule.

12. A host cell comprising the nucleic acid molecule of claim 11 or the vector of claim 12.

13. A cell line engineered to express the target-binding polypeptide of any one of claims 1 to 4 or the fusion protein of claim 5.

14. A chimeric antigen receptor (CAR), wherein the CAR comprises
(a) a targeting domain,
(b) a transmembrane domain, and
(c) an intracellular signaling domain,
wherein the targeting domain comprises the target-binding polypeptide of any one of claims 1 to 4 or the fusion protein of claim 5.

15. The CAR of claim 14, which is characterized by one or more of

(a) the intracellular signaling domain is selected from the group consisting of a human CD3 zeta domain, 41BB domain, a CD28 domain and any combination thereof,

(b) the target-binding polypeptide or fusion protein binds to a tumor antigen associated with a hematologic malignancy or a solid tumor,

(c) the target-binding polypeptide, DBDpp, or fusion protein binds to a tumor antigen selected from the group consisting of CD137, PD-L1, CD123, CTLA4, CD47, KIR, DR5, TIM3, PD1, EGFR, TCR, CD19, CD20, CD22, ROR 1, mesothelin, CD33/lL3Ra, cMet, PSMA, Glycolipid F77, EGFRvIII, GD2, NY-ESO- 1, MAGE A3, and combinations thereof,

(d) the intracellular signaling domain comprises a costimulatory signaling region, and

(e) the intracellular signaling domain comprises a costimulatory signaling region comprising the intracellular domain of a costimulatory molecule selected from the group consisting of CD27, CD28, 4-lBB, OX40, CD30, CD40, PD-1, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, a ligand that specifically binds with CD83, and any combination thereof.

16. An isolated nucleic acid molecule comprising a sequence encoding the CAR of claim 14 or claim 15.

17. A cell comprising a nucleic acid molecule comprising a sequence encoding the CAR of claim 14 or claim 15, optionally wherein the cell is a T cell or a natural killer (NK) cell, and optionally wherein the cell exhibits an anti-tumor immunity when the target-binding polypeptide or fusion protein binds to its corresponding tumor antigen..

18. Use of an immune cell comprising the CAR of claim 14 or claim 15 for the manufacture of a medicament for the treatment of cancer.

19. Use of an immune cell comprising a chimeric antigen receptor (CAR) for the manufacture of a medicament for the treatment of cancer, wherein the CAR comprises:

(a) a target binding domain comprising a target-binding polypeptide having an amino acid sequence selected from the group consisting of

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALGGSEAELAX_{30}FEX_{33}X_{34}IAX_{37}FEX_{40}X_{41}LQX_{44}YKGKGNPEVEALRKEAAAIRDELQAYRHN$ (SEQ ID NO:2), $MGSWAEFKQRLAAIKTRLEALGGSEAELAAFX_{32}X_{33}EIX_{36}AFX_{39}X_{40}ELX_{43}AYKGKGNPEVEALX_{57}X_{58}EAX_{61}AIX_{64}X_{65}ELX_{68}AYRHN$ (SEQ ID NO:3), $MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALGGSEAELAAFEKEIAAFESELQAYKGKGNPEVEX_{55}LRX_{58}X_{59}AAX_{62}IRX_{65}X_{66}LQAYRHN$ (SEQ ID NO:4), $MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALGGSEAELAAFX_{32}X_{33}EIX_{36}AFX_{39}X_{40}ELX_{43}AYKGKGNPEVEX_{55}LRX_{58}X_{59}AAX_{62}IRX_{65}X_{66}LQAYRHN$ (SEQ ID NO:5), and $MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALGGSEAELAX_{30}FEX_{33}X_{34}IAX_{37}FEX_{40}X_{41}LQX_{44}YKGKGNPEVEALX_{57}X_{58}EAX_{61}AIX_{64}X_{65}ELX_{68}AYRHN$ (SEQ ID NO:6), wherein X_n is a natural or non-natural amino acid, wherein X_n is not a cysteine or a proline residue, wherein the target-binding polypeptide specifically binds a target of interest expressed by a cancer cell, and wherein the specific binding of the target-binding polypeptide to the target of interest is greater than binding of a polypeptide according to SEQ ID NO:1 to the target of interest,

(b) a transmembrane domain selected from 41BB and CD28, and

(c) an intracellular domain, wherein the intracellular domain comprises a signaling domain selected from an alpha, beta, or zeta chain of the T cell receptor.

20. The use according to claim 18 or 19, wherein the immune cell is a T cell or a natural killer (NK) cell.

21. A method for transforming a reference polypeptide into a target-binding polypeptide capable of specifically binding to a target of interest, the method comprising:

(a) modifying a plurality of amino acid residues from the reference polypeptide to generate a plurality of candidate target-binding polypeptides; wherein the candidate target-binding polypeptides comprise a variant of the amino acid sequence of SEQ ID NO: 1, wherein the candidate target-binding polypeptides comprise three anti-parallel alpha helices joined by linker peptides, wherein the amino acid residues modified are solvent accessible or solvent inaccessible, and wherein the modification comprises one or more conservative or non-

conservative amino acid substitutions and does not include a substitution with a cysteine or a proline;

(b) packaging the plurality of candidate target-binding polypeptides in a plurality of vectors to generate a candidate library; and

(c) screening the candidate library for candidate target-binding polypeptides that exhibit specific binding to the target of interest,

wherein the candidate target-binding polypeptides comprise an amino acid sequence selected from the group consisting of

$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALGGSEAELAX_{30}FEX_{33}X_{34}IAX_{37}FEX_{40}X_{41}LQ$
$X_{44}YKGKGNPEVEALRKEAAAIRDELQAYRHN$ (SEQ ID NO:2),
$MGSWAEFKQRLAAIKTRLEALGGSEAELAAFX_{32}X_{33}EIX_{36}AFX_{39}X_{40}ELX_{43}AYKGKGNPE$
$VEALX_{57}X_{58}EAX_{61}AIX_{64}X_{65}ELX_{68}AYRHN$ (SEQ ID NO:3),
$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALGGSEAELAAFEKEIAAFESELQAYKGKGNPEV$
$EX_{55}LRX_{58}X_{59}AAX_{62}IRX_{65}X_{66}LQAYRHN$ (SEQ ID NO:4),
$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALGGSEAELAAFX_{32}X_{33}EIX_{36}AFX_{39}X_{40}ELX_{43}AYK$
$GKGNPEVEX_{55}LRX_{58}X_{59}AAX_{62}IRX_{65}X_{66}LQAYRHN$ (SEQ ID NO:5),
$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALGGSEAELAX_{30}FEX_{33}X_{34}IAX_{37}FEX_{40}X_{41}LQ$
$X_{44}YKGKGNPEVEALX_{57}X_{58}EAX_{61}AIX_{64}X_{65}ELX_{68}AYRHN$ (SEQ ID NO:6),
$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALZ_1EAELAX_{28}FEX_{31}X_{32}IAX_{35}FEX_{38}X_{39}LQX_{42}YZ_2$
$NPEVEALRKEAAAIRDELQAYRHN$ (SEQ ID NO:7),
$MGSWAEFKQRLAAIKTRLEALZ_1EAELAAFX_{30}X_{31}EIX_{34}AFX_{37}X_{38}ELX_{41}AYZ_2NPEVEALX$
$_{52}$ $X_{53}EAX_{56}AIX_{59}X_{60}ELX_{63}AYRHN$ (SEQ ID NO:8),
$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALZ_1EAELAAFEKEIAAFESELQAYZ_2NPEVE$
$X_{50}LRX_{53}X_{54}AAX_{57}IRX_{60}X_{61}LQAYRHN$ (SEQ ID NO:9),
$MGSWX_5X_6FKX_9X_{10}LAX_{13}IKX_{16}X_{17}LEALZ_1EAELAAFX_{30}X_{31}EIX_{34}AFX_{37}X_{38}ELX_{41}AYZ_2NP$
$EVEX_{50}LRX_{53}X_{54}AAX_{57}IRX_{60}X_{61}LQAYRHN$ (SEQ ID NO:10) and
$MGSWX_5EFX_8X_9RLX_{12}AIX_{15}X_{16}RLX_{19}ALZ_1EAELAX_{28}FEX_{31}X_{32}IAX_{35}FEX_{38}X_{39}LQX_{42}YZ_2N$
$PEVEALX_{52}X_{53}EAX_{56}AIX_{59}X_{60}ELX_{63}AYRHN$ (SEQ ID NO:11), wherein X_n is a natural or non-natural amino acid and Z_1 and Z_2 comprise between about 2 to about 30 natural or non-natural amino acids.

22. The method of claim 21, wherein the method further comprises identifying potentially immunogenic amino acid residues in a candidate target-binding polypeptide and modifying at least one of the potentially immunogenic amino acid residues in the candidate target-binding polypeptide, wherein the modification comprises an amino acid substitution.

23. Virus-like particles (VLPs) comprising a fusion polypeptide comprising the target-binding polypeptide of any one of claims 1 to 4, wherein the VLPs are suitable for use as immunogens for antibody generation, wherein said antibodies are directed against the target-binding polypeptide.