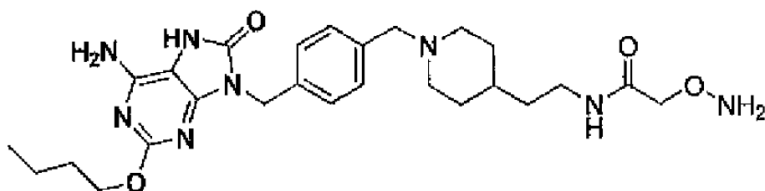


CLAIMS:

1. A composition comprising one or more targeting polypeptides having one or more non-natural amino acids incorporated, wherein at least one of said polypeptides is linked to a TLR agonist molecule via a linker covalently bonded to the non-natural amino acid of the targeting polypeptide, wherein the TLR agonist comprises a structure of:



or a salt thereof.

2. The composition of claim 1, wherein the one or more targeting polypeptides:
- (i) is a same targeting polypeptide,
 - (ii) binds to a cell surface target or tumor cell target, or
 - (iii) is a monospecific targeting polypeptide,
- optionally wherein the monospecific targeting polypeptide comprises a drug conjugate or checkpoint inhibitor.
3. The composition of claim 1, wherein the one or more targeting polypeptides is a bispecific, or multi-specific targeting polypeptide,
- optionally wherein the bispecific, or multi-specific targeting polypeptide comprises a drug conjugate or checkpoint inhibitor.
4. The composition of any one of claims 1-3, wherein the one or more targeting polypeptides comprises an antibody or antibody fragment.
5. The composition of claim 4, wherein the one or more targeting polypeptides is an antibody or antibody fragment that binds to an antigen of a cell, or
- wherein the one or more targeting polypeptides is an antibody or antibody fragment that binds to a target selected from the group consisting of HER2, HER3, PD-1, PDL-1, EGFR, TROP2, PSMA, VEGFR, CTLA-4, EpCAM, MUC1, MUC16, c-met, GPC3,

ENPP3, TIM-1, FOLR1, STEAP1, Mesothelin, 5T4, CEA, CA9, Cadherin 6, ROR1, SLC34A2, SLC39A6, SLC44A4, LY6E, DLL3, ePhA2, GPNMB, SLITRK6, CD3, CD19, CD22, CD24, CD25, CD30, CD33, CD38, CD44, CD47, CD52, CD56, CD70, CD96, CD97, CD99, CD117, CD123, CD179, CD223, and CD276.

6. The composition of claim 5, wherein the one or more targeting polypeptides comprises an antibody or antibody fragment that binds to HER2.

7. The composition of claim 6, wherein the one or more targeting polypeptides is trastuzumab.

8. The composition of claim 4, wherein the antibody or antibody fragment comprises an IgG, Fab, (Fab')₂, Fv, or single chain Fv (scFv),
one or more Fab, (Fab')₂, Fv, or single chain Fv (scFv) mutations,
one or more Fc mutations, or
one to six Fc mutations.

9. The composition of claim 4, wherein the antibody or antibody fragment comprises one or more non-natural amino acids incorporated in the heavy chain, light chain, or both the heavy and light chains.

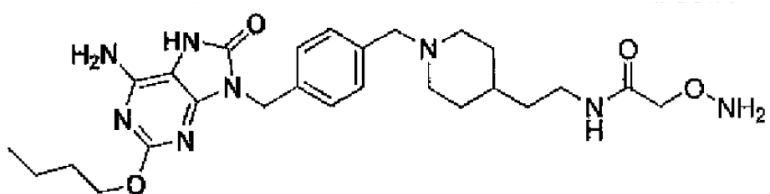
10. The composition of claim 9, wherein the antibody or antibody fragment further comprises one or more Fc mutations.

11. The composition of any one of claims 1-10, wherein the one or more targeting polypeptides is conjugated to one or more linker, polymer, or biologically active molecule.

12. The composition of claim 11, wherein the one or more linker is
(i) a non-cleavable linker,
(ii) 0.01kDa to 50kDa,
(iii) 0.01kDa to 10kDa,
(iv) linear,
(v) a bifunctional or multifunctional linker, or

- (vi) a PEG with a molecular weight between 0.1 kDa and 50 kDa.
13. The composition of claim 11, wherein the one or more polymer is
- (i) linear,
 - (ii) a bifunctional or multifunctional polymer,
 - (iii) a water soluble polymer,
- optionally wherein the water soluble polymer is polyethylene glycol (PEG),
optionally wherein the PEG has a molecular weight between 0.1kDa and 100kDa,
such as a molecular weight between 0.1kDa and 50kDa.
14. The composition of any one of claims 11-13, wherein at least one linker, polymer, or biologically active molecule is linked to at least one non-natural amino acids.
15. The composition of any one of claims 1-14, wherein the one or more targeting polypeptides comprises one or more amino acid substitution, addition or deletion that increases the stability or solubility of the composition.
16. The composition of any one of claims 1-15, wherein the one or more targeting polypeptides comprises one or more amino acid substitution, addition or deletion that increases the expression of the one or more targeting polypeptides in a recombinant host cell or synthesized *in vitro*.
17. The composition of any one of claims 1-16, wherein the non-natural amino acid is reactive toward a linker, polymer, or biologically active molecule that is otherwise unreactive toward any of the 20 common amino acids in the polypeptide,
- optionally wherein the non-natural amino acid comprises a carbonyl group, an aminooxy group, a hydrazine group, a hydrazide group, a semicarbazide group, an azide group, or an alkyne group,
 - optionally wherein the non-natural amino acid comprises a carbonyl group.
18. The composition of any one of claims 1-17, wherein the targeting polypeptide is linked to a cytotoxic agent or an immunostimulatory agent.

19. A TLR agonist conjugate (TC) comprising an anti-HER2 antibody or antibody fragment conjugated to a TLR agonist, wherein the TLR agonist is conjugated to the antibody or antibody fragment via a linker covalently bonded to one or more non-natural amino acids incorporated in the antibody or antibody fragment, and wherein the TLR agonist comprises a structure of:



, or a salt thereof.

20. The composition of any one of claims 1-18 or the TC of claim 19, wherein the non-natural amino acid is para-acetyl-phenylalanine, 4-azido-L-phenylalanine, para-azidomethyl-phenylalanine, para-azidoethoxy phenylalanine, or *p*-propargyloxy-L-phenylalanine;

optionally wherein the non-natural amino acid is para-acetyl phenylalanine;

and/or optionally wherein the non-natural amino acid is site-specifically incorporated into the one or more targeting polypeptide.

21. The TC of claim 19 or claim 20, wherein the linker is a non-cleavable linker, optionally wherein the linker is a bifunctional linker.

22. The composition of any one of claims 1-18 and 21, or the TC of any one of claims 19-21, wherein the antibody or antibody fragment comprises:

(i) the amino acid sequence of at least one of SEQ ID NOs: 1-13;

(ii) the amino acid sequence of at least two of SEQ ID NOs: 1-13;

(iii) a) SEQ ID NOs: 1 or 2; and b) any one of SEQ ID NOs: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13;

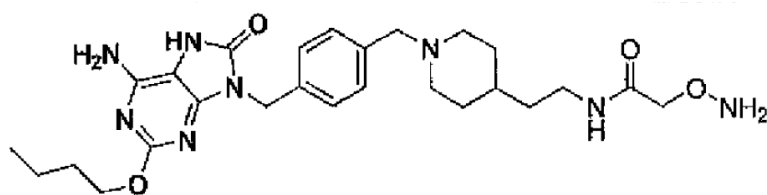
(iv) a) SEQ ID NO: 2; and b) any one of SEQ ID NOs: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13; or

(v) SEQ ID NO: 2 and SEQ ID NO: 3.

23. The TC of any one of claims 19-22, further comprising a chemotherapeutic or immunotherapeutic agent.

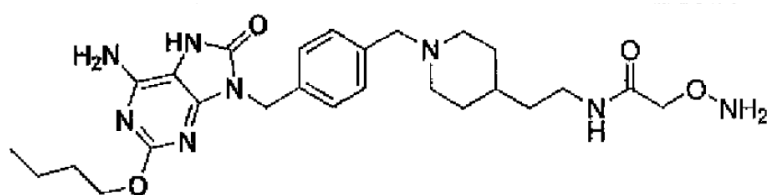
24. The composition of any one of claims 1-18, 20 and 22, or the TC of any one of claims 19-23, wherein the linker is a bond.

25. An immune stimulating antibody conjugate (ISAC) comprising a TLR agonist conjugate (TC) comprising an anti-HER2 antibody or antibody fragment conjugated to a TLR agonist, wherein the TLR agonist is conjugated to the antibody or antibody fragment via a linker covalently bonded to one or more non-natural amino acids incorporated in the antibody or antibody fragment, wherein the TLR agonist is of structure:



, or a salt thereof.

26. A compound having a structure of:



, or a salt thereof.

27. A pharmaceutical composition comprising a therapeutically-effective amount of the composition of any one of claims 1-18, 20, 22 and 24, the TC of any one of claims 19-24, the ISAC of claim 25, or the compound, or salt thereof, of claim 26, and a pharmaceutically acceptable carrier or excipient.

28. Use of the composition of any one of claims 1-18, 20, 22 and 24, the TC of any one of claims 19-24, the ISAC of claim 25, or the compound, or salt thereof, of claim 26 in the manufacture of a medicament for the treatment of a subject or patient having cancer.

29. Use of the composition, TC, ISAC, compound, or salt thereof, according to claim 28, wherein the treatment further comprises a chemotherapeutic or immunotherapeutic agent, or further comprises an antibody drug conjugate, a cytotoxic agent, or a checkpoint inhibitor.

30. A composition of any one of claims 1-18, 20, 22 and 24, the TC of any one of claims 19-24, the ISAC of claim 25, or the compound, or salt thereof, of claim 26 for use in therapy.