

therapeutic effect. Additional challenges exist due to the broad expression of the receptor for IL-21 (IL-21R). IL-21R is expressed not just on T cells, but also on B cells, NK cells and myeloid cells. Accordingly, care must be taken to limit broad IL-21 activation in leukocytes and avoid the potential for toxicity. Restriction of IL-21 signaling must be balanced and selective. Triggering the effects of IL-21 must be designed to occur at the right time and place.

[0007] Indeed, any success, especially clinical success with IL-21 moieties as a monotherapy or in combination with checkpoint inhibitors, has been muted. Thus, there remains a need for treatment modalities utilizing IL-21, including modalities combining IL-21 moieties with checkpoint inhibitors. There also remains a need for IL-21 therapies combined with immune checkpoint inhibition.

SUMMARY

[0007a] In one aspect, the present disclosure refers to a conjugate comprising an IL-21 mutein and an anti-PD-1 antibody, wherein the IL-21 mutein comprises the amino acid sequence of SEQ ID NO: 2, QGQDX HMXXM XXXXX XVDXL KNXVN DLVPE FLPAP EDVET NCEWS AFSCF QKAQL KSANT GNNEX XIXXX XXXLX XXXXX TNAGR RQKHR LTCPS CDSYE KKPPK EFLXX FXXLL XXMXX QHXSS RTHGS EDS (SEQ ID NO: 2), wherein “X” represents any amino acid, and wherein said IL-21 mutein amino acid sequence differs from the amino acid sequence of human IL-21 (SEQ ID NO: 1) by at least 1 amino acid.

[0007b] In another aspect, the present disclosure refers to a kit comprising the conjugate as disclosed herein, and a container.

[0007c] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the conjugate as disclosed herein, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0007d] In another aspect, the present disclosure refers to a use of the pharmaceutical composition as disclosed herein for use in the manufacture of a medicament for treating a subject having a solid tumor.

[0007e] In another aspect, the present disclosure refers to a pharmaceutical composition as disclosed herein for use in therapy for treating a subject in need thereof.

[0008] The present disclosure provides IL-21 muteins comprising the amino acid sequence of SEQ ID NO: 2, wherein SEQ ID NO: 2 is

QGQDX HMXXM XXXXX XVDXL KNXVN DLVPE FLPAP EDVET NCEWS
AFSCF QKAQL KSANT GNNEX XIXXX XXXLX XXXXX TNAGR RQKHR
LTCPS CDSYE KKPPK EFLXX FXXLL XXMXX QHXSS RTHGS EDS (SEQ ID
NO: 2), and X is any amino acid, and wherein the IL-21 mutein amino acid sequence
differs from the amino acid sequence of human IL-21 (SEQ ID NO: 1) by at least 1
amino acid.

[0009] Thus, in one example, the present disclosure also provides IL-21 muteins comprising only one amino acid substitution, relative to the wild-type IL-21 amino acid sequence, which is provided herein as SEQ ID NO: 1. In exemplary examples, the amino acid substitution is located at an amino acid position selected from the group consisting of: 5, 8, 9, 11, 12, 13, 14, 15, 16, 19, 23, 65, 66, 68, 69, 70, 72, 73, 75, 76, 77, 78, 79, 80, 109, 110, 112, 113, 116, 117, 119, 120, or 123, according to the amino acid position numbering of SEQ ID NO: 1.

[0010] The present disclosure further provides IL-21 muteins comprising only two amino acid substitutions, relative to SEQ ID NO: 1. In exemplary examples, the amino acid substitutions are located at two amino acid positions selected from the group consisting of: 5, 9, 15, 70, 71, 72, 73, and 76, according to the amino acid position numbering of SEQ ID NO: 1.

[0011] In exemplary examples, the IL-21 muteins bind to the IL-21 receptor (IL-21R) with a reduced affinity, relative to the affinity of wild-type IL-21 for the IL-21 receptor. In exemplary examples, the IL-21 mutein binds to the human IL-21R with a K_D that is greater than or is about 0.04 nM. In

WHAT IS CLAIMED IS:

1. A conjugate comprising an IL-21 mutein and an anti-PD-1 antibody, wherein the IL-21 mutein comprises the amino acid sequence of SEQ ID NO: 2,

QGQDX HMXXM XXXXX XVDXL KNXVN DLVPE FLPAP EDVET NCEWS
AFSCF QKAQL KSANT GNNEX XIXXX XXXLX XXXXX TNAGR RQKHR LTCPS
CDSYE KKPPK EFLXX FXXLL XXMXX QHXSS RTHGS EDS (SEQ ID NO: 2),

wherein “X” represents any amino acid, and wherein said IL-21 mutein amino acid sequence differs from the amino acid sequence of human IL-21 (SEQ ID NO: 1) by at least 1 amino acid.

2. The conjugate of claim 1, wherein the IL-21 mutein comprises an amino acid sequence which differs from the amino acid sequence of human IL-21 (SEQ ID NO: 1) by no more than 7 amino acids.
3. The conjugate of claim 1, wherein the IL-21 mutein comprises an amino acid sequence which differs from the amino acid sequence of human IL-21 (SEQ ID NO: 1) by 3, 4, 5, or 6 amino acids.
4. The conjugate of claim 1, wherein the IL-21 mutein comprises an amino acid sequence which differs from the amino acid sequence of human IL-21 (SEQ ID NO: 1) by 1 or 2 amino acids.
5. The conjugate of any one of the preceding claims, wherein (a) the difference(s) between the amino acid sequence of the IL-21 mutein and the amino acid sequence of SEQ ID NO: 1 occur(s) within (A) amino acids 10-15, inclusive, or amino acids 105-123, inclusive, of SEQ ID NO: 2, (b) the difference(s) occur(s) at amino acids 11, 14, 15, 109, 110, 112, 113, 116, 119, 120, and/or 123 of SEQ ID NO: 2 or (B) amino acids 5-25, inclusive, or amino acids 65-80, inclusive, of SEQ ID NO: 2, (c) the difference(s) occur(s) at amino acids 5, 8, 9, 12, 13, 16, 19, 23, 65, 66, 69, 70, 72, 73, 75, 76, 77, 78, 79, and/or 80 of SEQ ID NO: 2, or (d) any combination thereof.

6. The conjugate of any one of the preceding claims, wherein the IL-21 mutein comprises an amino acid sequence with one amino acid substitution relative to the amino acid sequence of human IL-21 (SEQ ID NO: 1).
7. The conjugate of claim 6, wherein the amino acid substitution occurs at position 5, 8, 9, 11, 12, 13, 14, 15, 16, 19, 23, 65, 66, 68, 69, 70, 71, 72, 73, 75, 76, 77, 78, 79, 80, 109, 110, 112, 113, 116, 117, 119, 120, or 123 of SEQ ID NO: 1.
8. The conjugate of any one of the preceding claims, wherein the IL-21 mutein comprises an amino acid substitution:
 - a. at position 5, 8, 9, 12, 14, 15, 65, 66, 69, 70, 72, 73, 75, 76, 77, 80, 116, or 119 of SEQ ID NO: 1, wherein the substitute amino acid is an aliphatic amino acid;
 - b. at position 5, 8, 9, 11, 12, 13, 14, 15, 16, 19, 23, 65, 66, 69, 70, 72, 73, 75, 76, 77, 78, 79, 110, 112, 116, 117, 119, 120, or 123 of SEQ ID NO: 1, wherein the substitute amino acid is an acidic amino acid;
 - c. at position 5, 9, 73, 76, 109, 113, or 116 of SEQ ID NO: 1, wherein the substitute amino acid is a basic amino acid;
 - d. at position 5, 8, 9, 70, or 76 of SEQ ID NO: 1, wherein the substitute amino acid is an aromatic amino acid;
 - e. at position 5, 8, 9, 12, 15, 73, 76, 116, or 119 of SEQ ID NO: 1, wherein the substitute amino acid is an amino acid comprising a side chain amide;
 - f. at position 5, 8, 9, 11, 12, 14, 15, 73, 76, 116, or 119 of SEQ ID NO: 1, wherein the substitute amino acid is a non-aromatic amino acid comprising a side chain hydroxyl;
 - g. at position 65, 66, 69, 70, 72, 73, 75, 76, 77, or 80 of SEQ ID NO: 1, wherein the substitute amino acid is an imino acid;

- h. at position 5, 9, 15, 76, 116, or 119 of SEQ ID NO: 1, wherein the substitute amino acid is an amino acid comprising a sulfur-containing side chain; or
- i. or a combination thereof.
9. The conjugate of any one of the preceding claims, wherein the IL-21 mutein comprises an amino acid substitution with an amino acid at the position according to TABLE A:

TABLE A

Amino Acid position of SEQ ID NO: 1	Amino Acid (in single letter code)	Amino Acid position of SEQ ID NO: 1	Amino Acid (in single letter code)
5	A, D, E, G, H, I, K, L, M, N, Q, S, T, V, or Y	72	D, G, or P
8	A, D, E, N, S, T, V, or Y	73	A, D, E, G, H, I, N, P, Q, S, or V
9	A, D, E, G, H, I, K, L, M, N, Q, S, T, V, or Y	75	D, G, or P
11	D or S	76	A, D, E, G, H, I, K, L, M, N, P, Q, S, T, V, or Y
12	A, D, E, N, S, T, or V	77	D, G, or P
13	D	78	D
14	A, D, or S	79	D
15	A, E, I, M, N, Q, S, T, or V	80	G, or P
16	D or E	109	K
19	D	110	D
23	D	112	D
65	D, G, or P	113	K
66	D, G, or P	116	A, D, E, I, K, L, M, N, S, T, or V
68	Q	117	D
69	D, G, or P	119	A, D, E, M, N, Q, S, or T
70	E, G, P, or Y	120	D
71	L	123	D

10. The conjugate of any one of the preceding claims, wherein the IL-21 mutein comprises:
- (a) an amino acid sequence of any one of SEQ ID NOs: 3-21, 23-56, 58-112, 114-

198, 249-254, and 283; or

(b) an amino acid sequence of any one of SEQ ID NOs: 199 to 208, 210 to 222, 224 to 248, and 255.

11. The conjugate of any one of the preceding claims, wherein (a) the IL-21 mutein comprises an amino acid sequence with two amino acid substitutions relative to the amino acid sequence of human IL-21 (SEQ ID NO: 1), or (b) the amino acid substitution occurs at two of positions 5, 8, 9, 11, 12, 13, 14, 15, 16, 19, 23, 65, 66, 68, 69, 70, 71, 72, 73, 75, 76, 77, 78, 79, 80, 109, 110, 112, 113, 116, 117, 119, 120, or 123 of SEQ ID NO: 1.
12. The conjugate of claim 11, wherein the amino acid substitution occurs at two of positions 5, 9, 73, and 76 of SEQ ID NO: 1.
13. The conjugate of any one of the preceding claims, wherein the IL-21 mutein comprises any two of the following:
 - an amino acid at position 5 of SEQ ID NO: 1, wherein said amino acid is selected from the group consisting of: A, D, E, G, H, I, K, L, M, N, Q, S, T, V, or Y;
 - an amino acid at position 9 of SEQ ID NO: 1, wherein said amino acid is selected from the group consisting of: A, D, E, G, H, I, K, L, M, N, Q, S, T, V, or Y;
 - an amino acid at position 73 of SEQ ID NO: 1, wherein said amino acid is selected from the group consisting of: A, D, E, G, H, I, N, P, Q, S, or V; and
 - an amino acid at position 76 of SEQ ID NO: 1, wherein said amino acid is selected from the group consisting of: A, D, E, G, H, I, K, L, M, N, P, Q, S, T, V, or Y.
14. The conjugate of any one of the preceding claims, wherein the IL-21 mutein comprises an amino acid substitution at position 5, 9, or 73 of SEQ ID NO: 1, wherein the substitute amino acid is selected from:

Amino Acid position of SEQ ID NO: 1	Amino Acid (in single letter code)
5	A, D, E, G, H, I, K, L, M, N, Q, S, T, V, or Y
9	A, D, E, G, H, I, K, L, M, N, Q, S, T, V, or Y
73	A, D, E, G, H, I, N, P, Q, S, or V

15. The conjugate of any one of the preceding claims, wherein the IL-21 mutein comprises an amino acid substitution at position 76 of SEQ ID NO: 1 and the substitute amino acid at position 76 is an aliphatic amino acid or an acidic amino acid.
16. The conjugate of claim 15, wherein the aliphatic amino acid is alanine or wherein the acidic amino acid is glutamic acid.
17. The conjugate of any one of the preceding claims, wherein the IL-21 mutein is directly attached to the Fc of the antibody.
18. The conjugate of any one of the preceding claims, wherein the IL-21 mutein is attached to the Fc of the antibody via a linker.
19. The conjugate of claim 17 or 18, wherein said conjugate comprises a single IL-21 mutein, wherein said single IL-21 mutein is linked to the C-terminus of one of the two antibody heavy chains.
20. The conjugate of claim 17 or 18, wherein said conjugate comprises two IL-21 muteins, wherein the first IL-21 mutein is linked to the C-terminus of the first antibody heavy chain, and the second IL-21 mutein is linked to the C-terminus of the second antibody heavy chain.
21. The conjugate of claim 20, wherein said first IL-21 mutein has the same amino acid sequence as the second IL-21 mutein.
22. The conjugate of claim 20, wherein said first IL-21 mutein and said second IL-21 mutein have the same amino acid sequence.

23. The conjugate of claim 20, wherein said first IL-21 mutein and said second IL-21 mutein have different amino acid sequences.
24. The conjugate of any one of the preceding claims, wherein the IL-21 mutein comprises an amino acid sequence of any one of SEQ ID NOs: 233-245.
25. The conjugate of claim 24, wherein the IL-21 mutein comprises an amino acid sequence of SEQ ID NO: 244.
26. The conjugate of claim 24, wherein the IL-21 mutein comprises an amino acid sequence of SEQ ID NO: 245.
27. The conjugate of any one of the preceding claims, wherein the conjugate is a fusion protein comprising an IL-21 mutein and an anti-PD-1 antibody.
28. The conjugate of claim 27, wherein the fusion protein comprises:
- (i) two light chains, each comprising the light chain of SEQ ID NO: 391, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of any one of SEQ ID NOs: 498-500 or 519; or
 - (ii) two light chains, each comprising the light chain of SEQ ID NO: 391, a heavy chain fused to an IL-21 mutein comprising the heavy chain fused to an IL-21 mutein of any one of SEQ ID NOs: 501-506, and a heavy chain comprising the heavy chain of any one of SEQ ID NOs: 556-558; or
 - (iii) two light chains, each comprising the light chain of SEQ ID NO: 371, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of any one of SEQ ID NOs: 508-512; or
 - (iv) two light chains, each comprising the light chain of SEQ ID NO: 371, a heavy chain fused to an IL-21 mutein comprising an amino acid sequence of any one of SEQ ID NOs: 513-518, and a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 559-561;

- (v) two light chains, each comprising the light chain variable region of SEQ ID NO: 389, and
two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of any one of SEQ ID NOs: 498-500 or 519; or
- (vi) two light chains, each comprising the light chain variable region of SEQ ID NO: 389,
a heavy chain fused to an IL-21 mutein comprising the heavy chain fused to an IL-21 mutein of any one of SEQ ID NOs: 501-506, and
a heavy chain comprising the heavy chain of any one of SEQ ID NOs: 556-558; or
- (vii) two light chains, each comprising the light chain variable region of SEQ ID NO: 369, and
two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of any one of SEQ ID NOs: 508-512; or
- (viii) two light chains, each comprising the light chain variable region of SEQ ID NO: 369,
a heavy chain fused to an IL-21 mutein comprising the heavy chain fused to an IL-21 mutein of any one of SEQ ID NOs: 513-518, and
a heavy chain comprising the heavy chain of any one of SEQ ID NOs: 559-561; or
- (ix) two light chains, each comprising a light chain variable region of SEQ ID NO: 389 and a light chain constant region of SEQ ID NO: 391, and
two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of any one of SEQ ID NOs: 498-500 or 519; or
- (x) two light chains, each comprising a light chain variable region of SEQ ID NO: 389 and a light chain constant region of SEQ ID NO: 391,
a heavy chain fused to an IL-21 mutein comprising the heavy chain fused to an IL-21 mutein of any one of SEQ ID NOs: 501-506, and
a heavy chain comprising the heavy chain of any one of SEQ ID NOs: 556-558; or

(xi) two light chains, each comprising a light chain variable region of SEQ ID NO: 369 and a light chain constant region of SEQ ID NO: 371, and

two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of any one of SEQ ID NOs: 508-512; or

(xii) two light chains, each comprising a light chain variable region of SEQ ID NO: 369 and a light chain constant region of SEQ ID NO: 371,

a heavy chain fused to an IL-21 mutein comprising the heavy chain fused to an IL-21 mutein of any one of SEQ ID NOs: 513-518, and

a heavy chain comprising the heavy chain of any one of SEQ ID NOs: 559-561.

29. The conjugate of claim 1, wherein the conjugate is a fusion protein comprising an IL-21 mutein and an anti-PD-1 antibody, wherein the fusion protein comprises:

(i) two light chains, each comprising a LC CDR1, LC CDR2, and LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 385, 386, and 387, respectively;

(ii) two heavy chains, each comprising a HC CDR1, HC CDR2, and HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 382, 383, and 384, respectively; and

(iii) an IL-21 mutein comprising the amino acid sequence of SEQ ID NO: 244, wherein the IL 21 is fused to one of the antibody heavy chains.

30. The conjugate of claim 29, wherein each light chain comprises the light chain variable region of SEQ ID NO: 389 and each heavy chain comprises the heavy chain variable region of SEQ ID NO: 388.

31. The conjugate of claim 1, wherein the conjugate is a fusion protein comprising an IL-21 mutein and an anti-PD-1 antibody, wherein the fusion protein comprises:

(i) two light chains, each comprising the light chain of SEQ ID NO: 391;

(ii) one heavy chain comprising the heavy chain of SEQ ID NO: 556; and

(iii) one heavy chain fused to an IL-21 mutein comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 501.

32. The conjugate of claim 1, wherein the conjugate is a fusion protein comprising an IL-21 mutein and an anti-PD-1 antibody, wherein:

- (a) the fusion protein comprises:
 - (i) two light chains, each comprising the light chain variable region of SEQ ID NO: 389;
 - (ii) one heavy chain comprising the heavy chain of SEQ ID NO: 556; and
 - (iii) one heavy chain fused to an IL-21 mutein comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 501; or
- (b) the fusion protein comprises:
 - (i) two light chains, each comprising the light chain variable region of SEQ ID NO: 389 and the light chain constant region of SEQ ID NO: 391;
 - (ii) one heavy chain comprising the heavy chain of SEQ ID NO: 556; and
 - (iii) one heavy chain fused to an IL-21 mutein comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 501.

33. The conjugate of claim 1, wherein the conjugate is a fusion protein comprising an IL-21 mutein and an anti-PD-1 antibody, wherein the fusion protein comprises:

- (i) two light chains, each comprising the light chain of SEQ ID NO: 391, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 499, or
- (ii) two light chains, each comprising the light chain variable region of SEQ ID NO: 389, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 499, or
- (iii) two light chains, each comprising the light chain variable region of SEQ ID NO: 389 and the light chain constant region of SEQ ID NO: 391, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 499, or

(iv) two light chains, each comprising the light chain of SEQ ID NO: 391, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 519; or

(v) two light chains, each comprising the light chain variable region of SEQ ID NO: 389, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 519; or

(vi) two light chains, each comprising the light chain variable region of SEQ ID NO: 389 and the light chain constant region of SEQ ID NO: 391, and two heavy chain-IL-21 mutein fusions, each comprising the amino acid sequence of SEQ ID NO: 519.

34. The conjugate of claim 1, wherein the conjugate is a fusion protein comprising an IL-21 mutein and an anti-PD-1 antibody, wherein the fusion protein comprises:

(i) two light chains, each comprising a LC CDR1, LC CDR2, and LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 365, 366, and 367, respectively;

(ii) two heavy chains, each comprising a HC CDR1, HC CDR2, and HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 362, 363, and 364, respectively; and

(iii) an IL-21 mutein comprising the amino acid sequence of SEQ ID NO: 244, wherein the IL 21 is fused to one of the antibody heavy chains.

35. The conjugate of claim 34, wherein each light chain comprises the light chain variable region of SEQ ID NO: 369 and each heavy chain comprises the heavy chain variable region of SEQ ID NO: 368.

36. The conjugate of claim 1, wherein the conjugate is a fusion protein comprising an IL-21 mutein and an anti-PD-1 antibody, wherein:

(a) the fusion protein comprises:

(i) two light chains, each comprising the light chain of SEQ ID NO: 371;

- (ii) one heavy chain comprising the heavy chain of SEQ ID NO: 559; and
 - (iii) one heavy chain fused to an IL-21 mutein comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 513; or
- (b) the fusion protein comprises:
 - (i) two light chains, each comprising the light chain variable region of SEQ ID NO: 369;
 - (ii) one heavy chain comprising the heavy chain of SEQ ID NO: 559; and
 - (iii) one heavy chain fused to an IL-21 mutein comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 513; or
- (c) the fusion protein comprises:
 - (i) two light chains, each comprising the light chain variable region of SEQ ID NO: 369 and the light chain constant region of SEQ ID NO: 371;
 - (ii) one heavy chain comprising the heavy chain of SEQ ID NO: 559; and
 - (iii) one heavy chain fused to an IL-21 mutein comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 513.

37. The conjugate of claim 1, wherein the conjugate is a fusion protein comprising an IL-21 mutein and an anti-PD-1 antibody, wherein the fusion protein comprises:

- (i) two light chains, each comprising the light chain of SEQ ID NO: 371, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 508, or
- (ii) two light chains, each comprising the light chain variable region of SEQ ID NO: 369, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 508, or
- (iii) two light chains, each comprising the light chain variable region of SEQ ID NO: 369 and the light chain constant region of SEQ ID NO: 371, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 508, or

(iv) two light chains, each comprising the light chain of SEQ ID NO: 371, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 511; or

(v) two light chains, each comprising the light chain variable region of SEQ ID NO: 369, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 511; or

(vi) two light chains, each comprising the light chain variable region of SEQ ID NO: 369 and the light chain constant region of SEQ ID NO: 371, and two heavy chain-IL-21 mutein fusions, each comprising the heavy chain fused to an IL-21 mutein of SEQ ID NO: 511.

38. A kit comprising the conjugate of any one of the preceding claims and a container.

39. A pharmaceutical composition comprising the conjugate of any one of the preceding claims and a pharmaceutically acceptable carrier, excipient, or diluent.

40. The pharmaceutical composition of claim 39 for use in therapy for treating a subject in need thereof.

41. Use of the pharmaceutical composition of claim 40 for use in the manufacture of a medicament for treating a subject having a solid tumor.