

CLAIMS

1. A method of modifying T cell activity in a subject with cancer and/or treating a cancer, the method comprising:
 - administering to a subject a composition comprising:
 - a vector comprising a promoter operatively linked to a nucleic acid sequence encoding a chimeric antigen receptor (CAR), or
 - T cells expressing the CAR (CAR-T cells),
 - wherein the CAR is directed to a first targeting moiety, a second targeting moiety, or both the first and second targeting moieties;
 - administering to the subject one or more adaptor compounds, or pharmaceutically acceptable salts thereof, each adaptor compound or pharmaceutically acceptable salt thereof comprising a small molecule ligand linked to the first targeting moiety; and
 - administering to the subject an activity modifying compound linked to the second targeting moiety.
2. The method of claim 1, wherein the small molecule ligand is linked to the first targeting moiety by a first linker.
3. The method of claim 1 or claim 2, wherein the one or more adaptor compounds, or pharmaceutically acceptable salts thereof, comprise at least:
 - a first set of adaptor compounds or pharmaceutically acceptable salts thereof, each adaptor compound or pharmaceutically acceptable salt thereof of the first set comprising a first small molecule ligand linked to the first targeting moiety; and
 - a second set of adaptor compounds or pharmaceutically acceptable salts thereof, each adaptor compound or pharmaceutically acceptable salt thereof of the second set comprising a second small molecule ligand linked to the first targeting moiety;
 - wherein the first small molecule ligand is specific to a receptor overexpressed on a first type of cancer cell and the second small molecule ligand is specific to a receptor overexpressed on a second type of cancer cell.
4. The method of claim 1 or claim 2, wherein the activity modifying compound is linked to the second targeting moiety by a second linker.
5. The method of claim 1, wherein the activity modifying compound comprises:
 - a rejuvenating compound, or a pharmaceutically acceptable salt thereof, formulated to rejuvenate exhausted CAR-T cells; or
 - an immunosuppressive compound, or a pharmaceutically acceptable salt thereof, formulated to reduce the activity of the CAR-T cells.

6. The method of claims 1, 2, or 5, wherein the activity modifying compound, or the pharmaceutically acceptable salt thereof, comprises an immunosuppressive compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of tacrolimus, sirolimus, and cyclosporine.

7. The method of claim 1 or claim 2, wherein the first targeting moiety and the second targeting moiety have the same structure.

8. The method of claim 1, wherein the small molecule ligand is linked to the first targeting moiety by a first linker, the activity modifying compound is linked to the second targeting moiety by a second linker, and the first linker and the second linker are the same.

9. The method of claim 1, wherein the small molecule ligand is linked to the first targeting moiety by a first linker, the activity modifying compound is linked to the second targeting moiety by a second linker, and the first linker and the second linker are different.

10. The method of any one of claims 1, 2, or 5, wherein the CAR has a recognition region comprising a single chain fragment variable (scFv) region of an antibody that binds to the first targeting moiety or the second targeting moiety with high affinity.

11. The method of claim 10, wherein the one or more of the adaptor compounds or the pharmaceutically acceptable salts thereof, and the activity modifying compound each bind to the scFv region of the CAR with an affinity in the sub-nanomolar range.

12. The method of claim 1, wherein the activity modifying compound comprises a rejuvenating compound, or a pharmaceutically acceptable salt thereof, and is formulated to block inhibitory signaling of exhausted CAR-T cells, reactivate the exhausted CAR-T cells through an antigen independent pathway, or both.

13. The method of claim 10, wherein binding the recognition region of a CAR-T cell to the second targeting moiety linked to the activity modifying compound internalizes the activity modifying compound into the CAR-T cell.

14. The method of any one of claims 1, 2, or 5, wherein the small molecule ligand of each of the one or more adaptor compounds is specific to a receptor overexpressed on a targeted cancer cell as compared to normal tissue or a non-targeted cancer cell.

15. The method of any one of claims 1, 2, or 5, wherein the small molecule ligand is selected from the group consisting of a folate, a 2-{3-[(1,3-dicarboxypropyl)ureido]pentanedioic acid (DUPA) ligand, a neurokinin 1 receptor (NK-1R) ligand, a carbonic anhydrase IX (CAIX) ligand, a ligand of gamma glutamyl transpeptidase, a natural killer group 2D receptor (NKG2D) ligand, and a cholecystokinin B receptor (CCKBR or CCK2) ligand.

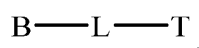
16. The method of any one of claims 1, 2, or 5, wherein the first targeting moiety and the second targeting moiety are each independently selected from the group consisting of 2,4-dinitrophenol (DNP), 2,4,6-trinitrophenol (TNP), biotin, digoxigenin, fluorescein, fluorescein isothiocyanate (FITC), NHS-fluorescein, pentafluorophenyl ester, tetrafluorophenyl ester, knottin, centyrin, and DARPin.

17. The method of claim 8 or claim 9, wherein the first linker and second linker are each independently a releasable linker or a non-releasable linker.

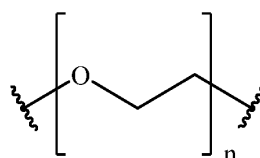
18. The method of claim 8 or claim 9, wherein the first linker, the second linker, or both independently comprise a C₁-C₂₀ alkyl, a polyethylene glycol (PEG), a polyproline, an oligo-(4-piperidine carboxylic acid, an oligo piperidine, a peptide, a saccharo-peptide, a hydrophilic amino acid, a sugar, an unnatural peptidoglycan, a polyvinylpyrrolidone, pluronic F-127, or a combination thereof.

19. The method of claim 8 or claim 9, wherein the first linker or the second linker comprises PEG.

20. The method of any one of claims 1, 2, 5 or 12, wherein the one or more adaptor compounds, or the pharmaceutically acceptable salts thereof, each has the formula:



where B represents the small molecule ligand, L represents the first linker, and T represents the first targeting moiety, and L comprises a structure having the formula:

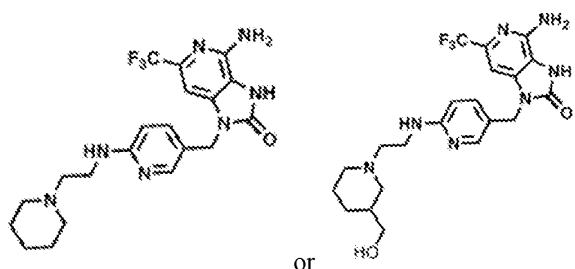


where n is an integer from 0 to 200.

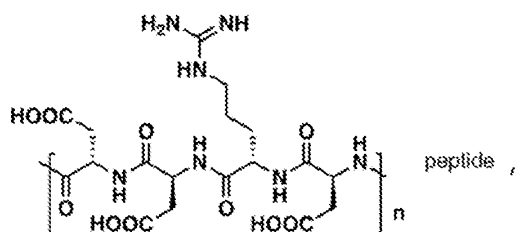
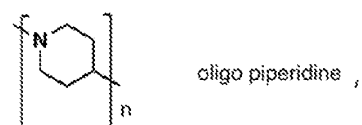
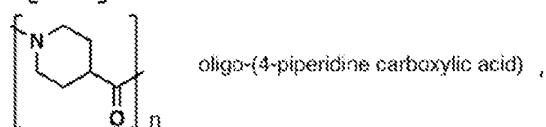
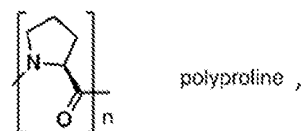
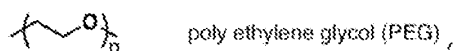
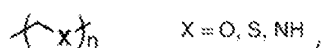
21. The method of claim 12, wherein the rejuvenating compound, or the pharmaceutically acceptable salt thereof, is selected from the group consisting of a Toll-Like Receptor (TLR) agonist, a stimulator of interferon genes agonist, a phosphatase inhibitor, a Nod-like receptor stimulant, an absent in melanoma 2-like receptor agonist, a kinase inhibitor, a retinoic acid-inducible gene-I-like receptor, and a receptor for advanced glycation end products.

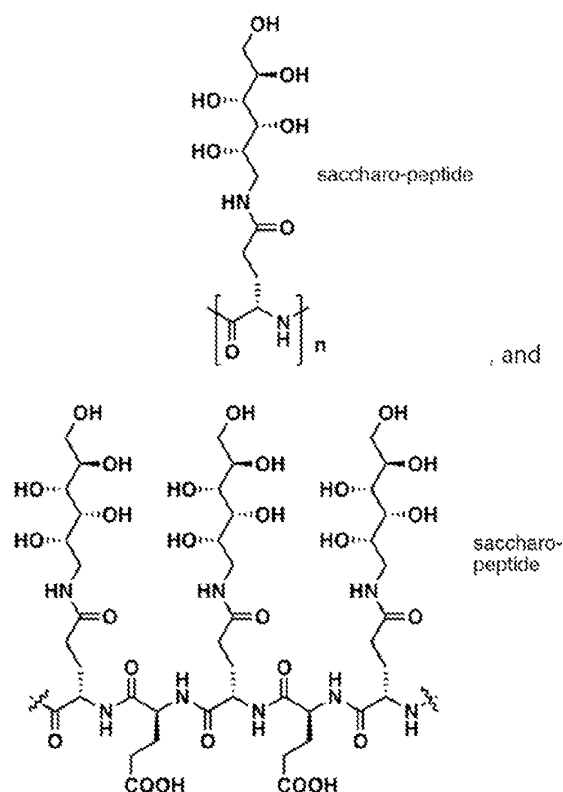
22. The method of claim 21, wherein the rejuvenating compound, or the pharmaceutically acceptable salt thereof, is a TLR7 or a TLR7/8 agonist.

23. The method of claim 22, wherein the rejuvenating compound has one of the following formulae:



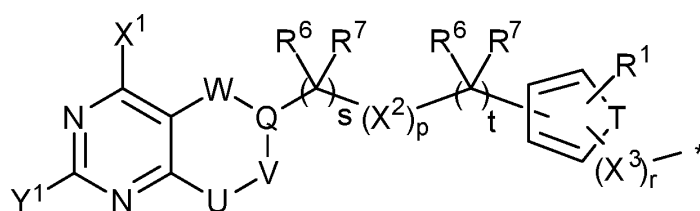
24. The method of claim 2, wherein the first linker in the one or more adaptor compounds, or the pharmaceutically acceptable salts thereof, is positioned between the small molecule ligand and the first targeting moiety and comprises a chemical moiety having a structure selected from the following formulae:





wherein n is an integer from 0 to 200.

25. The method of claim 1 or 24, wherein the small molecule ligand of the one or more adaptor compounds, or the pharmaceutical acceptable salts thereof, comprises a structure having the formula:



wherein:

X¹ and Y¹ are each independently selected from the group consisting of a halo, R², OR², SR³, and NR⁴R⁵;

U, V, and W represent divalent moieties each independently selected from the group consisting of -(R^{6a})C=, -N=, -(R^{6a})C(R^{7a})-, and -N(R^{4a})-;

Q is selected from the group consisting of C and CH;

T is selected from the group consisting of S, O, N, and $-C=C-$;

X^2 and X^3 are each independently selected from the group consisting of oxygen, sulfur, $-C(Z)-$, $-C(Z)O-$, $-OC(Z)-$, $-N(R^{4b})-$, $-C(Z)N(R^{4b})-$, $-N(R^{4b})C(Z)-$, $-OC(Z)N(R^{4b})-$, $-N(R^{4b})C(Z)O-$, $-N(R^{4b})C(Z)N(R^{5b})-$, $-S(O)-$, $-S(O)_2-$, $-N(R^{4a})S(O)_2-$, $-C(R^{6b})(R^{7b})-$, $-N(C\equiv CH)-$, $-N(CH_2C\equiv CH)-$, C_1-C_{12} alkylene, and C_1-C_{12} alkyneoxy, where Z is oxygen or sulfur;

R^1 is selected from the group consisting of hydrogen, halo, C_1-C_{12} alkyl, and C_1-C_{12} alkoxy;

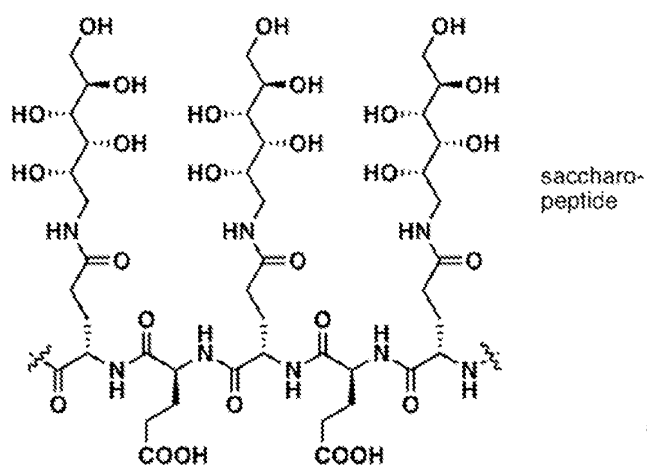
R^2 , R^3 , R^4 , R^{4a} , R^{4b} , R^5 , R^{5b} , R^{6b} , and R^{7b} are each independently selected from the group consisting of hydrogen, halo, C_1-C_{12} alkyl, C_1-C_{12} alkoxy, C_1-C_{12} alkanoyl, C_1-C_{12} alkenyl, C_1-C_{12} alkynyl, $(C_1-C_{12}$ alkoxy)carbonyl, and $(C_1-C_{12}$ alkylamino)carbonyl;

R^6 and R^7 are each independently selected from the group consisting of hydrogen, halo, C_1-C_{12} alkyl, and C_1-C_{12} alkoxy; or, R^6 and R^7 are taken together to form a carbonyl group;

R^{6a} and R^{7a} are each independently selected from the group consisting of hydrogen, halo, C_1-C_{12} alkyl, and C_1-C_{12} alkoxy; or R^{6a} and R^{7a} are taken together to form a carbonyl group;

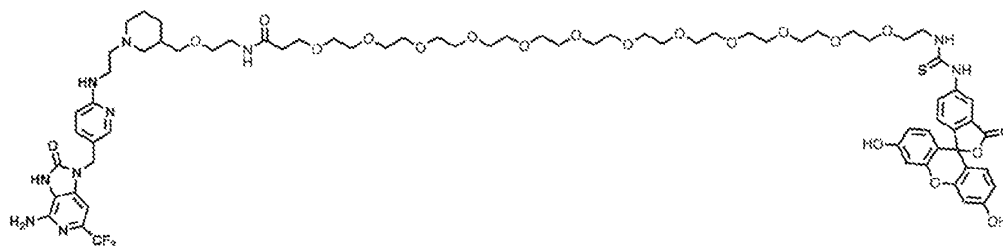
p, r, s, and t are each independently either 0 or 1; and

* represents a covalent bond, if the one or more adaptor compound, or pharmaceutically acceptable salt thereof, comprises a chemical moiety.

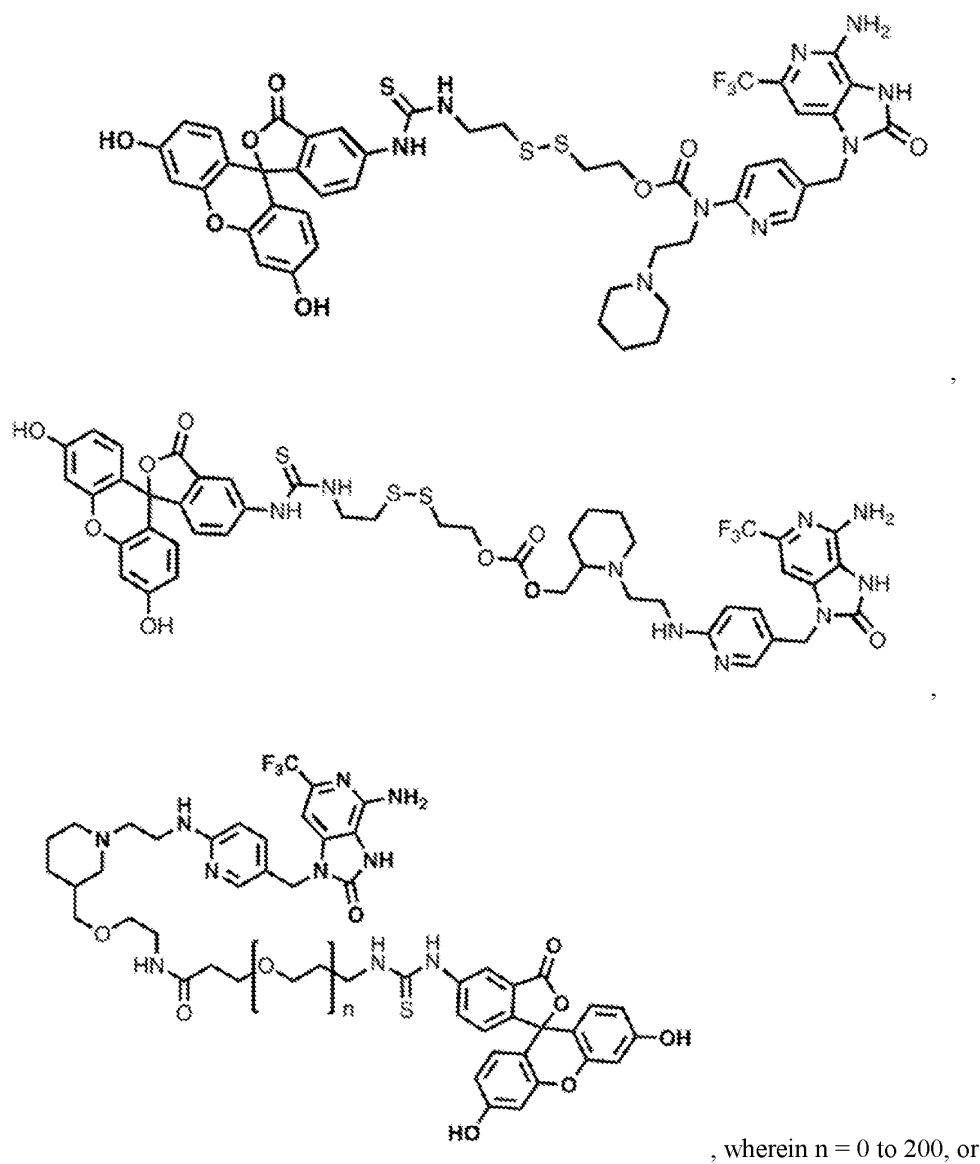


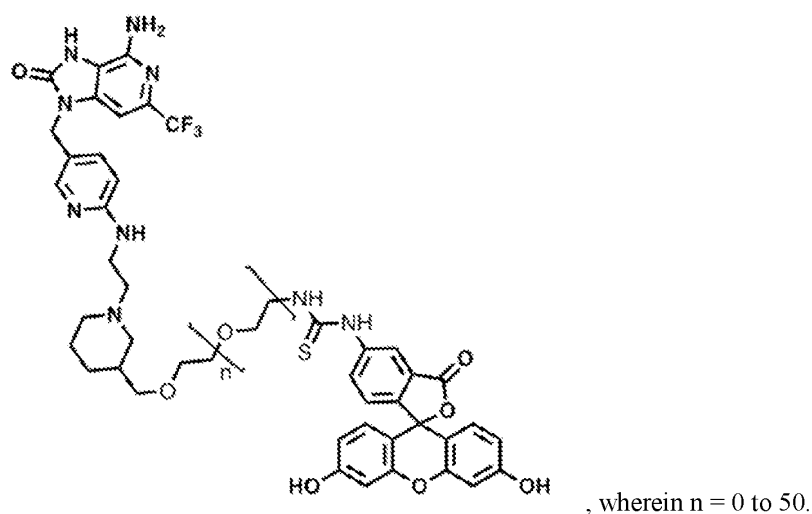
wherein n is an integer from 0 to 200.

27. The method of any one of claims 5, 12, 21, or 22, wherein the rejuvenating compound or the pharmaceutically acceptable salt thereof has the following formula:



28. The method of any one of claims 5, 12, 21, or 22, wherein the rejuvenating compound or the pharmaceutically acceptable salt thereof has a structure of one of the following formulae:





29. The method of any one of claims 1, 2, 5, or 21-23, wherein each of the one or more adaptor compounds or the pharmaceutically acceptable salt thereof, or the activity modifying compound is administered at a dose of about 10 nmoles/kg to about 10,000 nmoles/kg of body weight of the subject.

30. The method of any one of claims 1, 2, 5, or 21-23, wherein each of the one or more adaptor compounds or the pharmaceutically acceptable salt thereof, or the activity modifying compound is administered at a dose of about 10 nmoles/kg to about 2,000 nmoles/kg of body weight of the subject.

31. The method of any one of claims 1, 2, 5, or 21-23, wherein each of the one or more adaptor compounds or the pharmaceutically acceptable salt thereof, or the activity modifying compound is administered at a dose of about 10 nmoles/kg to about 1,000 nmoles/kg of body weight of the subject.

32. The method of any one of claims 1, 2, 5, or 21-23, wherein each of the one or more adaptor compounds or the pharmaceutically acceptable salt thereof, or the activity modifying compound is administered at a dose of about 10 nmoles/kg to about 600 nmoles/kg of body weight of the subject.

33. The method of any one of claims 1, 2, 5, or 21-23, wherein each of the one or more adaptor compounds or the pharmaceutically acceptable salt thereof, or the activity modifying compound is administered at a dose of about 200 nmoles/kg to about 600 nmoles/kg of body weight of the subject.

34. The method of any one of claims 1, 2, 5, or 21-23, wherein each of the one or more adaptor compounds or the pharmaceutically acceptable salt thereof, or the activity

modifying compound is administered at a dose of about 250 nmoles/kg to about 600 nmoles/kg of body weight of the subject.

35. The method of claim 1, wherein the cancer is lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head, cancer of the neck, cutaneous melanoma, intraocular melanoma, uterine cancer, ovarian cancer, endometrial cancer, rectal cancer, stomach cancer, colon cancer, breast cancer, triple negative breast cancer, carcinoma of the fallopian tubes, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, prostate cancer, leukemia, pleural mesothelioma, cancer of the bladder, Burkitt's lymphoma, cancer of the ureter, cancer of the kidney, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or adenocarcinoma of the gastroesophageal junction.

36. The method of any one of claims 1, 2, 5, or 21-23, wherein the CAR comprises a recognition region that is a scFv region of an anti-FITC antibody.

37. The method of claim 1, wherein the CAR further comprises a co-stimulation domain selected from the group consisting of CD28, CD137 (4-1BB), CD134 (OX40), and CD278 (ICOS).

38. The method of claim 1, wherein the CAR further comprises an activation signaling domain that is a T cell CD3 ζ chain or an Fc receptor γ .

39. The method of any one of claims 1, 2, 5, or 21-23, further comprising:
imaging the subject prior to administering the one or more adaptor compounds, or the pharmaceutically acceptable salts thereof, or prior to administering the CAR-T cell composition.

40. The method of any one of claims 1, 2, 5, or 21-23, wherein at least one of the one or more adaptor compounds, or the pharmaceutically acceptable salts thereof, is not an antibody nor comprises a fragment of an antibody.

41. The method of any one of claims 1, 2, 5, or 21-23, wherein one or both of the first targeting moiety and the second targeting moiety do not comprise a peptide epitope.

42. The method of claim 1, wherein the vector comprises a lentiviral vector.

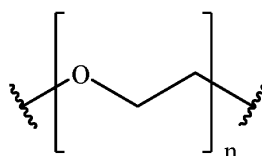
43. A method of treating a subject having received CAR-T cell therapy comprising:
administering to the subject one or more adaptor compounds, or pharmaceutically acceptable salts thereof, each adaptor compound or pharmaceutically acceptable salt thereof comprising a small molecule ligand linked to a first targeting moiety;

wherein, prior to the administering step, the subject has received at least a dose of T cells expressing a chimeric antigen receptor (CAR) that recognizes and binds to the first targeting moiety.

44. The method of claim 43, further comprising administering to the subject an activity modifying compound linked to a second targeting moiety, wherein the CAR recognizes and binds to the second targeting moiety.

45. The method of claim 43 or claim 44, wherein the small molecular ligand of each adaptor compound is linked to the first targeting moiety via a first linker.

46. The method of claim 45, wherein the first linker comprises a structure having the formula:

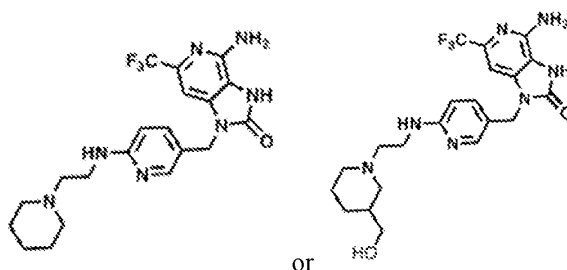


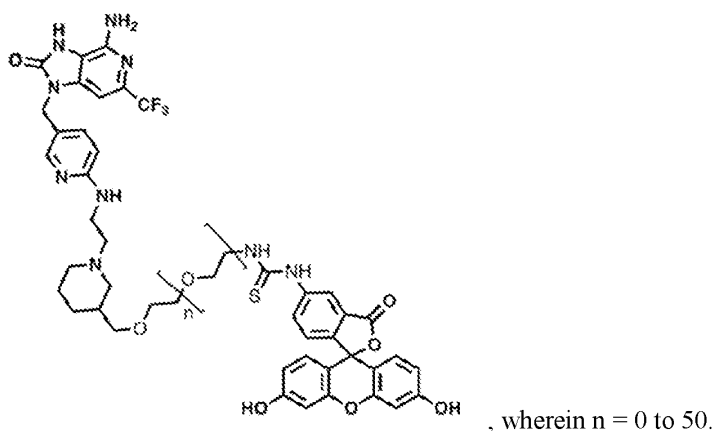
wherein n is an integer from 0 to 200.

47. The method of claim 44, wherein the activity modifying compound is linked to the second targeting moiety by a second linker.

48. The method of claim 44 or claim 47, wherein the activity modifying compound comprises a rejuvenating compound, or a pharmaceutically acceptable salt thereof, linked to the second targeting moiety, wherein the rejuvenating compound, or the pharmaceutically acceptable salt thereof, is selected from the group comprising a Toll-Like Receptor (TLR) agonist, a stimulator of interferon genes agonist, a phosphatase inhibitor, a Nod-like receptor stimulant, an absent in melanoma 2-like receptor agonist, a kinase inhibitor a retinoic acid-inducible gene-I-like receptor, and a receptor for advanced glycation end products.

49. The method of claim 48, wherein the rejuvenating compound, or the pharmaceutically acceptable salt thereof, is a TLR7 agonist having a structure of one of the following formulae:





52. A combination for modifying T cell activity in a subject with cancer, wherein the combination comprises:

one or more adaptor compounds, or pharmaceutically acceptable salts thereof, wherein each adaptor compound, or pharmaceutically acceptable salt thereof, comprises a small molecule ligand linked to a first targeting moiety; and

an activity modify compound linked to a second targeting moiety, the activity modify compound comprising:

a rejuvenating compound, or a pharmaceutically acceptable salt thereof, or

an immunosuppressive compound, or a pharmaceutically acceptable salt thereof.

53. The combination of claim 52, the one or more adaptor compounds, or pharmaceutically acceptable salts thereof, comprise at least:

a first set of adaptor compounds, each comprising a first small molecule ligand linked to the first targeting moiety, the first small molecule ligand specific to a receptor overexpressed on a first type of cancer cell as compared to a non-targeted type of cell; and

a second set of adaptor compounds, each comprising a second small molecule ligand linked to the first targeting moiety, the second small molecule ligand specific to a receptor overexpressed on a second type of cancer cell as compared to a non-targeted type of cell.

54. The combination of claim 52 or claim 53, wherein the first targeting moiety and the second targeting moiety have the same structure.

55. The combination of claim 52 or claim 53, wherein the first targeting moiety and the second targeting moiety have the different structures.

56. The combination of claim 52, wherein at least one of the one or more adaptor compounds, or pharmaceutically acceptable salts thereof, further comprises a first linker positioned between the small molecule ligand and the first targeting moiety.

57. The combination of claim 52, wherein a second linker is positioned between the second targeting moiety and the activity modifying compound.

58. The combination of claim 56, wherein a second linker is positioned between the second targeting moiety and the activity modifying compound and the first linker and the second linker have the same structure or different structures.

59. The combination of claim 52, further comprising a composition comprising:
a vector comprising a promoter operatively linked to a nucleic acid sequence encoding a chimeric antigen receptor (CAR); or
T cells expressing the CAR (CAR-T cells);
wherein the CAR is directed to the first targeting moiety, the second targeting moiety, or both the first and second targeting moieties.

60. The combination of claim 59, wherein the CAR has a recognition region comprising a single chain fragment variable (scFv) region of an antibody that binds to the first targeting moiety and the second targeting moiety with high affinity.

61. The combination of claim 60, wherein the first and second targeting moieties bind to the scFv region with an affinity in the sub-nanomolar range.

62. The combination of any one of claims 52, 53, or 55-58, wherein the small molecule ligand is selected from a group consisting of: a folate, a 2-{3-[(1,3-dicarboxypropyl)ureido]pentanedioic acid (DUPA) ligand, a neurokinin 1 receptor (NK-1R) ligand, a carbonic anhydrase IX (CAIX) ligand, a ligand of gamma glutamyl transpeptidase, a natural killer group 2D receptor (NKG2D) ligand, and a cholecystokinin B receptor (CCKBR or CCK2) ligand.

63. The combination of any one of claims 52, 53, or 55-58, wherein the first targeting moiety, the second targeting moiety, or both the first and second targeting moieties are independently selected from a group consisting of: 2,4-dinitrophenol (DNP), 2,4,6-trinitrophenol (TNP), biotin, digoxigenin, fluorescein, fluorescein isothiocyanate (FITC), NHS-fluorescein, pentafluorophenyl ester, tetrafluorophenyl ester, a knottin, a centyrin, and a DARPin.

64. The combination of claim 58, wherein at least one of the first linker and the second linker is a releasable linker.

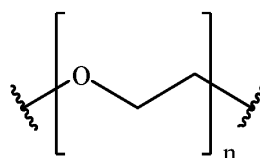
65. The combination of claim 58, wherein at least one of the first linker and the second linker is a non-releasable linker.

66. The combination of claim 58, wherein the first linker, the second linker, or both the first and second linkers each independently comprises a C₁-C₂₀ alkyl, a polyethylene glycol

(PEG), a polyproline, an oligo-(4-piperidine carboxylic acid, an oligo piperidine, a peptide, a saccharo-peptide, a hydrophilic amino acid, a sugar, an unnatural peptidoglycan, a polyvinylpyrrolidone, pluronic F-127, or a combination thereof.

67. The combination of claim 66, wherein at least the first linker or the second linker comprises PEG.

68. The combination of claim 58, wherein at least one of the first linker and the second linker comprises a structure having the formula:

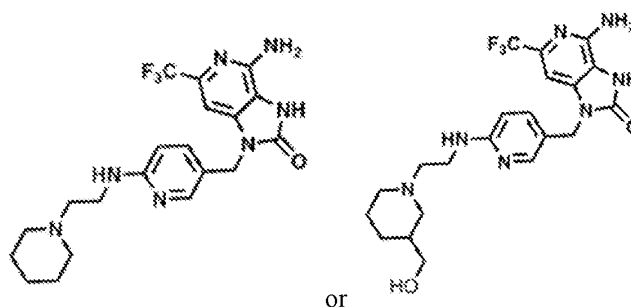


wherein n is an integer from 0 to 200.

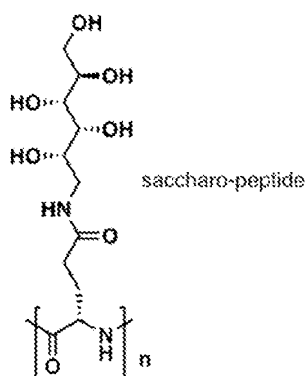
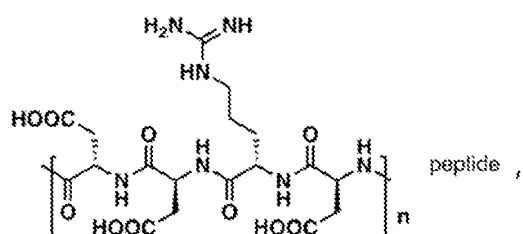
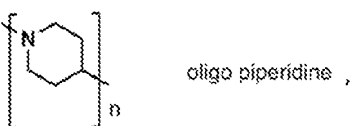
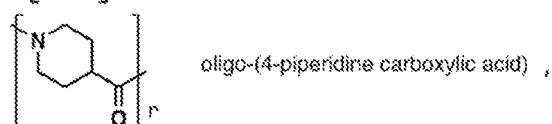
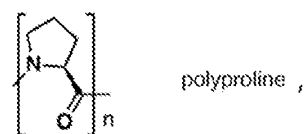
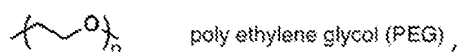
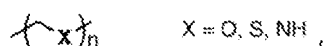
69. The combination of claim 52, wherein the rejuvenating compound, or the pharmaceutically acceptable salt thereof, is selected from a group comprising a Toll-Like Receptor (TLR) agonist, a stimulator of interferon genes agonist, and a phosphatase inhibitor, a Nod-like receptor stimulant, an absent in melanoma 2-like receptor agonist, a kinase inhibitor, a retinoic acid-inducible gene-I-like receptor, and a receptor for advanced glycation end products.

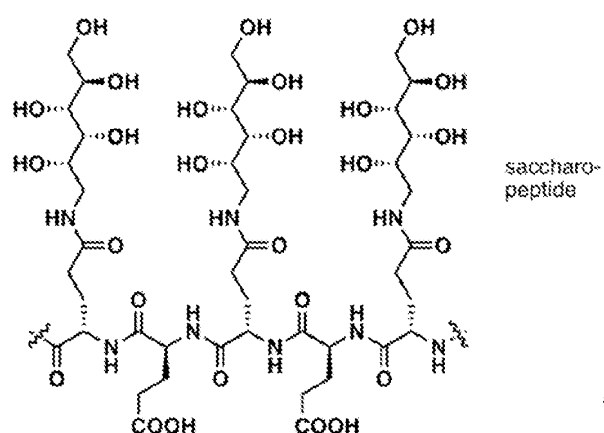
70. The combination of claim 69, wherein the rejuvenating compound, or the pharmaceutically acceptable salt thereof, is a TLR7 agonist.

71. The combination of claim 70, wherein the TLR7 agonist has the formula



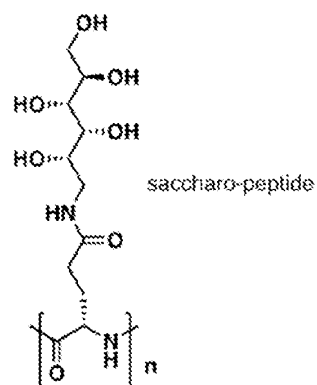
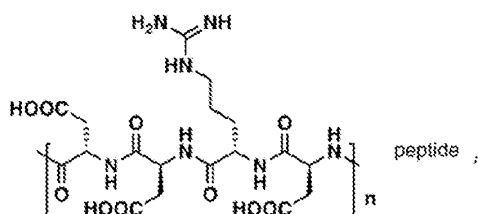
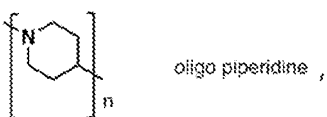
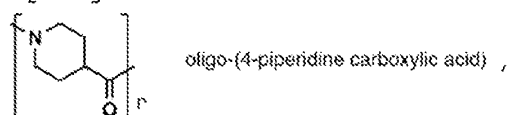
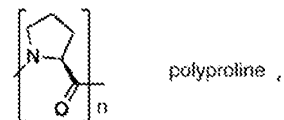
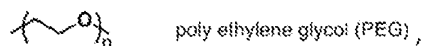
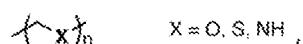
72. The combination of claim 56 or claim 58, wherein the first linker in the one or more adaptor compounds, or the pharmaceutically acceptable salts thereof, is positioned between the small molecule ligand and the first targeting moiety and comprises one or more structures selected from the following formulae: \



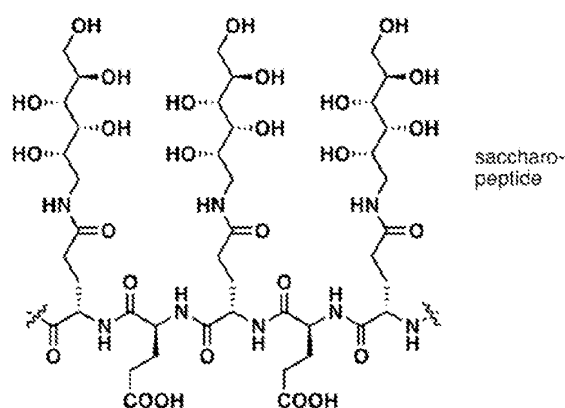


wherein n is an integer from 0 to 200.

73. The combination of claim 57 or claim 58, wherein the second linker is positioned between the second targeting moiety and the activity modifying compound, or the pharmaceutically acceptable salt thereof, and comprises one or more structures selected from the following formulae:



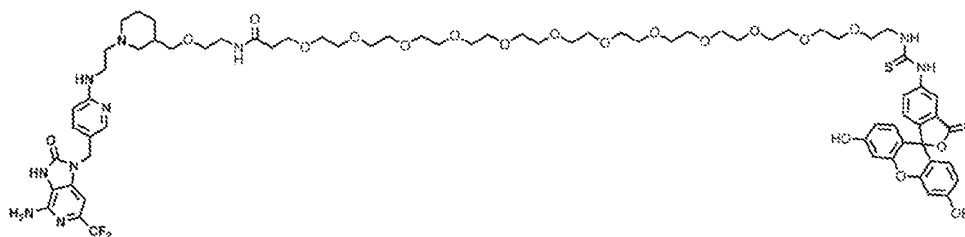
, and



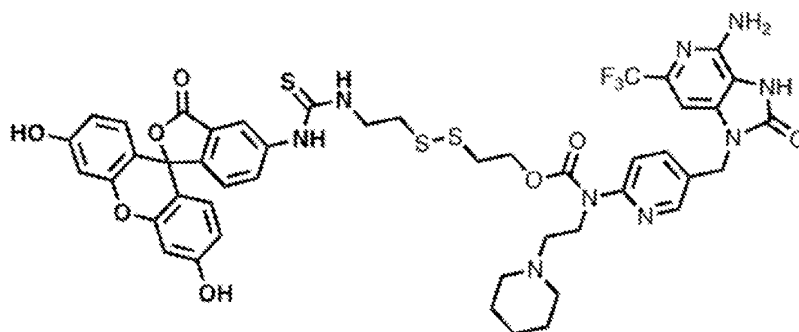
wherein n is an integer from 0 to 200.

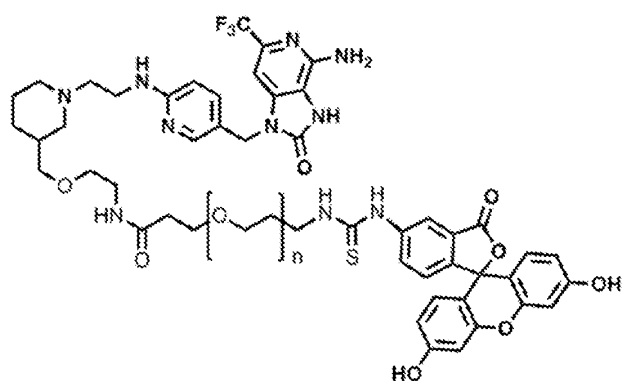
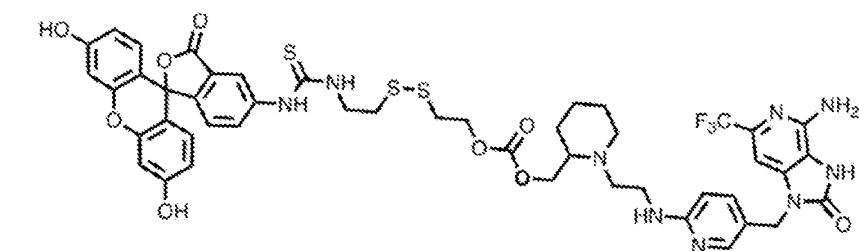
wherein n is an integer from 0 to 200.

74. The combination of any one of claims 52 or 69-71, wherein the rejuvenating compound, or the pharmaceutically acceptable salt thereof, has the formula:

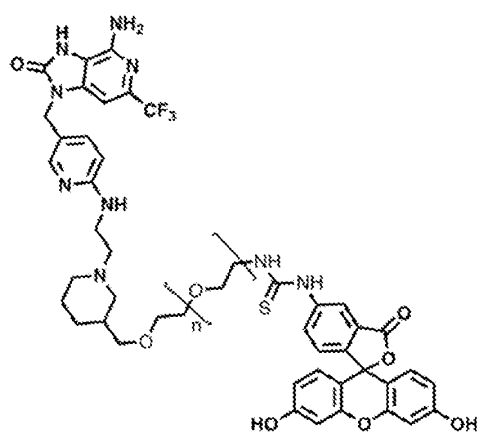


75. The combination of any one of claims 52 or 69-71, wherein the rejuvenating compound, or the pharmaceutically acceptable salt thereof, has a structure of one of the following formulae:





, wherein $n = 0$ to 200, and



, wherein $n = 0$ to 50.

76. The combination of claim 60 or claim 61, wherein the scFv region of the antibody is a scFv region of an anti-FITC antibody.

77. The combination of any one of claims 59-61, wherein the CAR further comprises a co-stimulation domain selected from a group consisting of CD28, CD137 (4-1BB), CD134 (OX40), and CD278 (ICOS).

78. The combination of any one of claims 59-61, wherein the CAR further comprises an activation signaling domain.

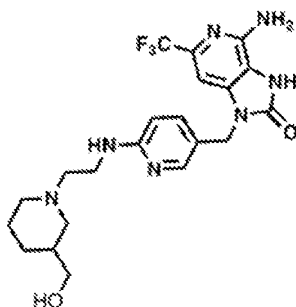
79. The combination of claim 78, wherein the activation signaling domain is a T cell CD3 ζ chain or an Fc receptor γ .

80. The combination of claim 52, wherein each adaptor compound, or the pharmaceutically acceptable salt thereof, is not an antibody, and does not comprise a fragment of an antibody.

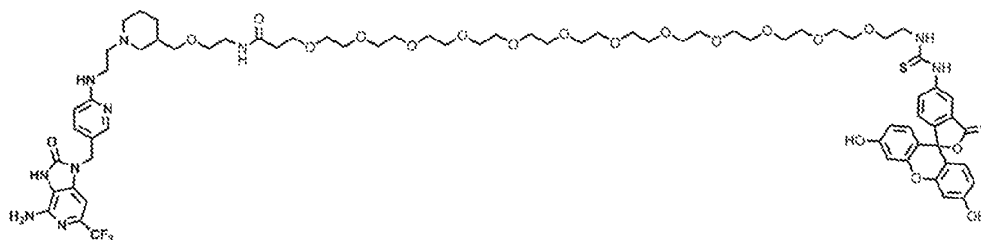
81. The combination of claim 52, wherein the first targeting moiety does not comprise a peptide epitope.

82. A compound for rejuvenating T cells expressing chimeric antigen receptor, the compound comprising a rejuvenating compound, or a pharmaceutically acceptable salt thereof, linked to a targeting moiety, wherein the rejuvenating compound, or the pharmaceutically acceptable salt thereof, is selected from the group consisting of a Toll-Like Receptor (TLR) agonist, a stimulator of interferon genes agonist, a phosphatase inhibitor, a Nod-like receptor stimulant, an absent in melanoma 2-like receptor agonist, a kinase inhibitor, retinoic acid-inducible gene-I-like receptor, and a receptor for advanced glycation end products.

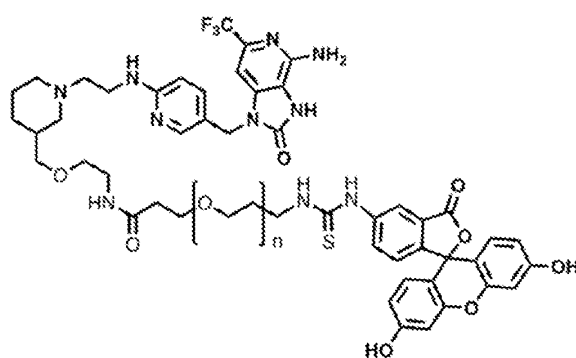
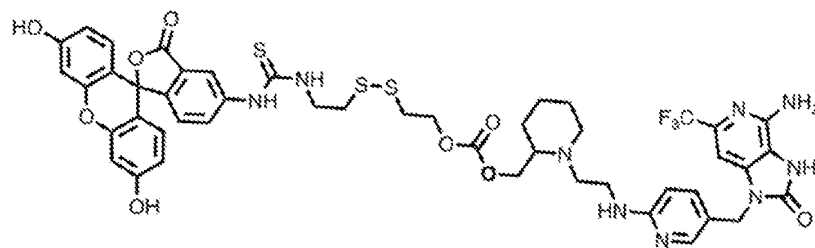
83. The compound of claim 82, wherein the rejuvenating compound, or the pharmaceutically acceptable salt thereof, has a structure of the following formula:



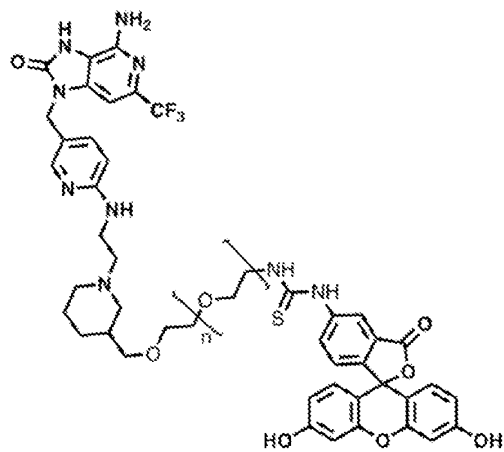
84. The compound of claim 82 or claim 83, wherein the rejuvenating compound or pharmaceutically acceptable salt thereof, has a structure of the following formula:



85. The compound of claim 82 or claim 83, wherein the rejuvenating compound, or pharmaceutically acceptable salt thereof, has a structure of one of the following formulae:

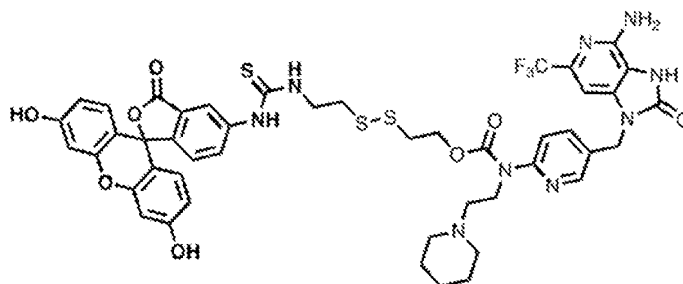


, wherein $n = 0$ to 200, and



, wherein $n = 0$ to 50.

86. The compound of claim 82, wherein the rejuvenating compound, or pharmaceutically acceptable salt thereof, has the following formula:



87. The compound of any one of claims 82-86, wherein the targeting moiety is selected from the group consisting of 2,4-dinitrophenol (DNP), 2,4,6-trinitrophenol (TNP), biotin, digoxigenin, fluorescein, fluorescein isothiocyanate (FITC), NHS-fluorescein, pentafluorophenyl ester (PFP), tetrafluorophenyl ester (TFP), a knottin, a centyrin, and a designed ankyrin repeat protein (DARPin).