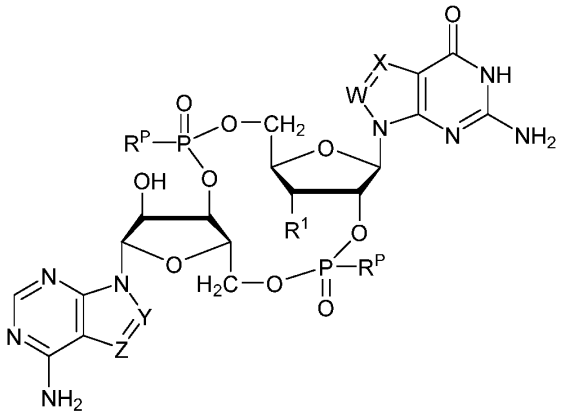
CLAIMS

1. An antibody-drug conjugate (ADC) having the structure of Formula Ia:

(Formula Ia) Ab-[-L-D]$_n$

wherein:

"D" represents a cyclic di-nucleotide (CDN) having the structure of Formula IIk:



Formula IIk

wherein

W, X, Y, and Z are independently CH or N;

R^1 is C_{2-4}alkyl substituted with a thiol, amino, or C_{1-6}alkylamino group;

R^p is, independently for each occurrence, hydroxyl, thiol, C_{1-6}alkyl, borano (-BH_3^-), or –NR'R", wherein R' and R" are, independently for each occurrence, hydrogen or C_{1-6}alkyl optionally substituted with one or more groups selected from halogen, thiol, hydroxyl, carboxyl, C_{1-6}alkoxy, C_{1-6}hydroxyalkoxy, -OC(O)C_{1-6}alkyl, -N(H)C(O)C_{1-6}alkyl, -N(C_{1-3}alkyl)C(O)C_{1-6}alkyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, oxo, and azido; or R' and R" on the same nitrogen together form a C_{3-5}heterocyclic ring;

or a pharmaceutically acceptable salt thereof;

"Ab" represents an antibody or binding fragment thereof which binds a target antigen;

"L" represents, independently for each occurrence, a linker linking one or more occurrences of D to Ab;

"n" represents the number of occurrences of D linked to Ab via the linker (L);

wherein the CDN (D) is covalently bound to linker (L) at the thiol, amino, or C_{1-6}alkylamino group at the R^1 position of the CDN.

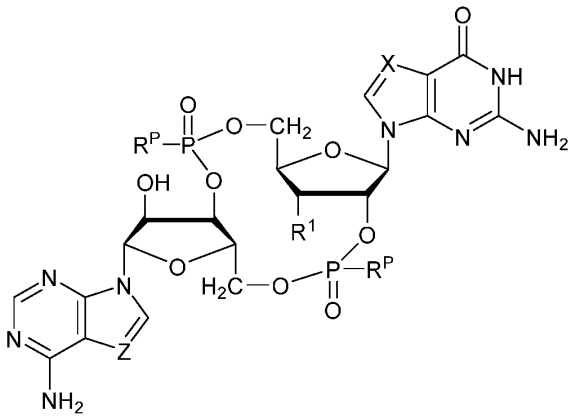
2. The ADC of claim 1, wherein R^1 is C_{2-4}alkyl substituted with an amino group.

3. The ADC of claim 1, wherein R^1 is C_{2-4}alkyl substituted with a C_{1-6}alkylamino group

4. The ADC of claim 1, wherein R^1 is C_{2-4}alkyl substituted with a methylamino group.

5. The ADC of claim 1, wherein R^1 is C_{2-4}alkyl substituted with a thiol group.

6. The ADC of claim 1, wherein D is a CDN having the structure of Formula IIm:



Formula IIm

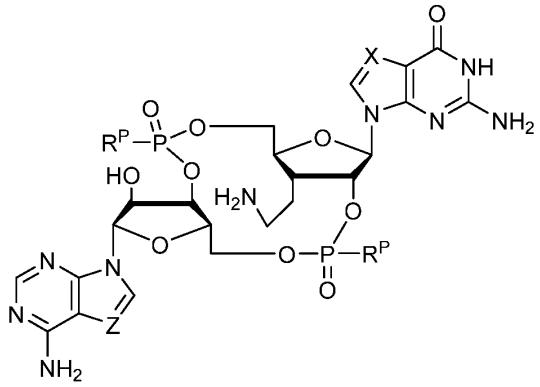
wherein

R^1 is ethyl substituted with a thiol, amino, or C_{1-6}alkylamino group; and

R^P, independently for each occurrence, is hydroxyl or thiol;

or a pharmaceutically acceptable salt thereof.

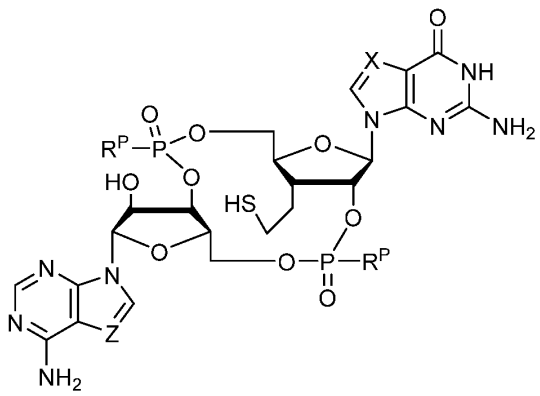
7. The ADC of claim 6, wherein the ADC is derived from a structure of Formula IIn:



Formula IIn

or a pharmaceutically acceptable salt thereof.

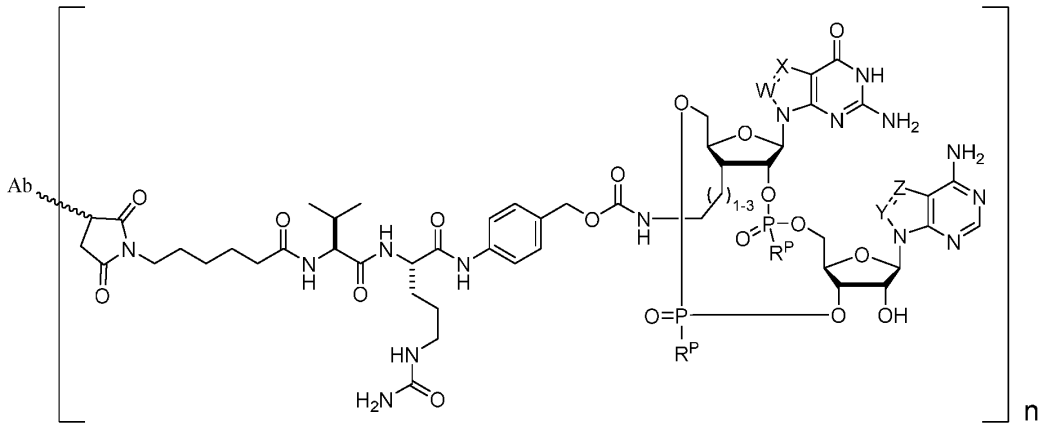
8. The ADC of claim 6, wherein the ADC is derived from a structure of Formula IIo:



Formula IIo

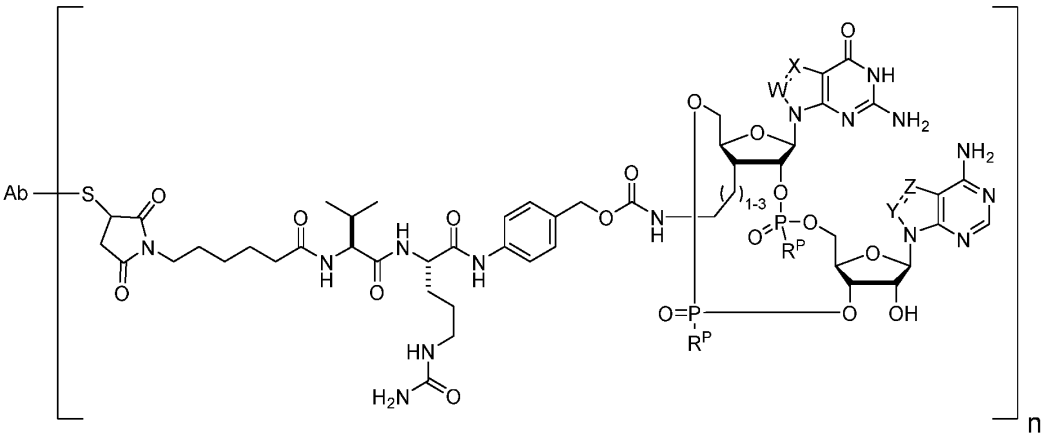
or a pharmaceutically acceptable salt thereof.

9. The ADC of claim 1, wherein the ADC has the structure of Formula III:



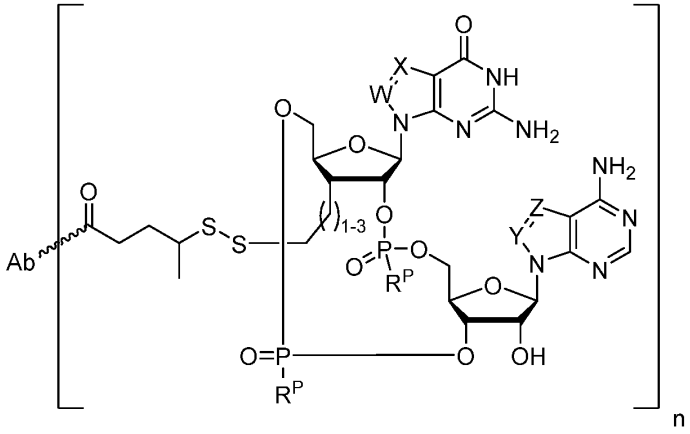
Formula III.

10. The ADC of claim 1, wherein the ADC has the structure of Formula IIIa:



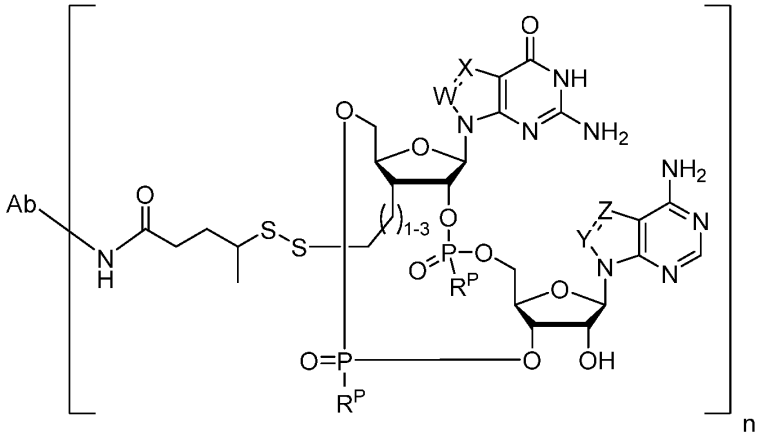
Formula IIIa.

11. The ADC of claim 1, wherein the ADC has the structure of Formula IV:



Formula IV.

12. The ADC of claim 1, wherein the ADC has the structure of Formula IVa:



Formula IVa.

13. The ADC of any one of claims 1-12, wherein X and Z are N.

14. The ADC of any one of claims 1-12, wherein X and Z are CH.

15. The ADC of any one of claims 1-12, wherein X is N and Z is CH.

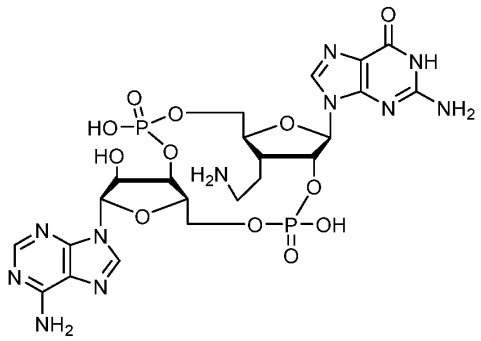
16. The ADC of any one of claims 1-15, wherein R^P, independently for each occurrence, is hydroxyl or thiol.

17. The ADC of claim 16, wherein both occurrences of R^P are hydroxyl.

18. The ADC of claim 16, wherein both occurrences of R^P are thiol.

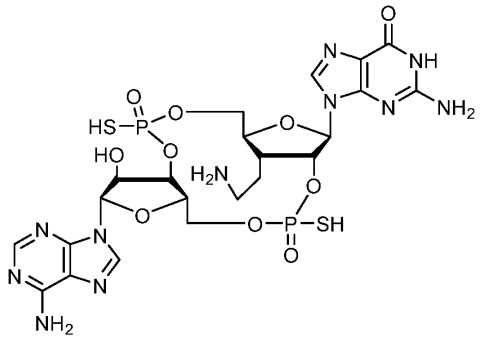
19. The ADC of claim 16, wherein one occurrence of R^P is hydroxyl and the other is thiol.

20. The ADC of claim 1, wherein the ADC is derived from a CDN with the following structure:



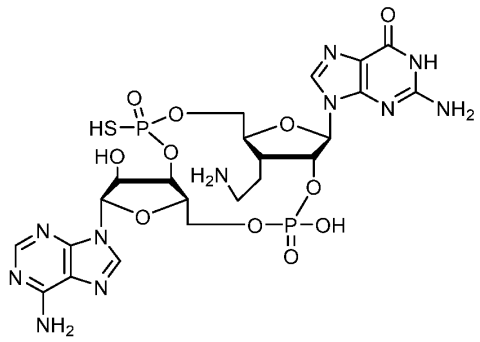
or a pharmaceutically acceptable salt thereof.

21. The ADC of claim 1, wherein the ADC is derived from a CDN with the following structure:



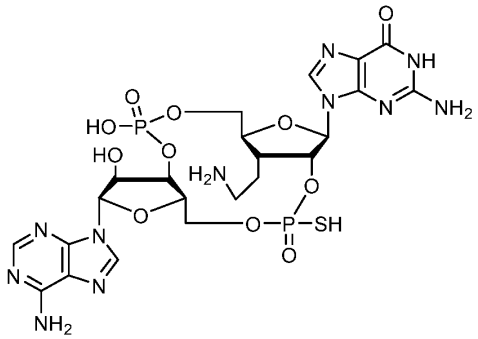
or a pharmaceutically acceptable salt thereof.

22. The ADC of claim 1, wherein the ADC is derived from a CDN with the following structure:



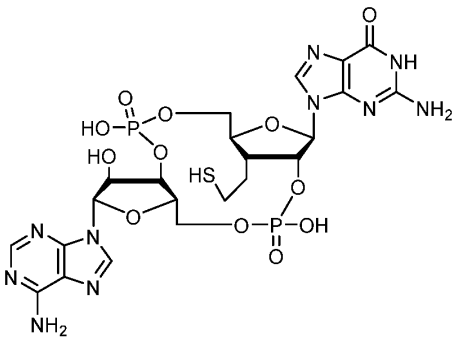
or a pharmaceutically acceptable salt thereof.

23. The ADC of claim 1, wherein the ADC is derived from a CDN with the following structure:



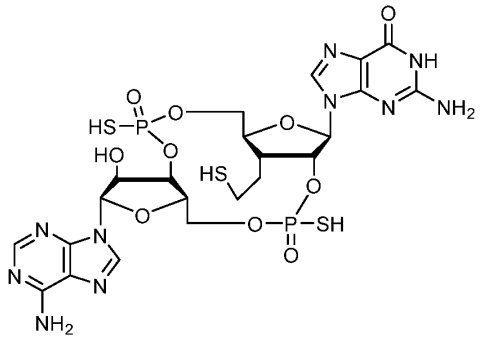
or a pharmaceutically acceptable salt thereof.

24. The ADC of claim 1, wherein the ADC is derived from a CDN with the following structure:



or a pharmaceutically acceptable salt thereof.

25. The ADC of claim 1, wherein the ADC is derived from a CDN with the following structure:



or a pharmaceutically acceptable salt thereof.

26. The ADC of any one of claims 1-25, wherein L comprises one or more cleavable linkers.

27 The ADC of claim 26, wherein the cleavable linker is an acid-cleavable linker.

28. The ADC of claim 26, wherein the cleavable linker is a hydrazone or hydrazine containing linker.

29. The ADC of claim 26, wherein the cleavable linker is a reducible linker.

30. The ADC of claim 29, wherein the reducible linker is a disulfide linker.

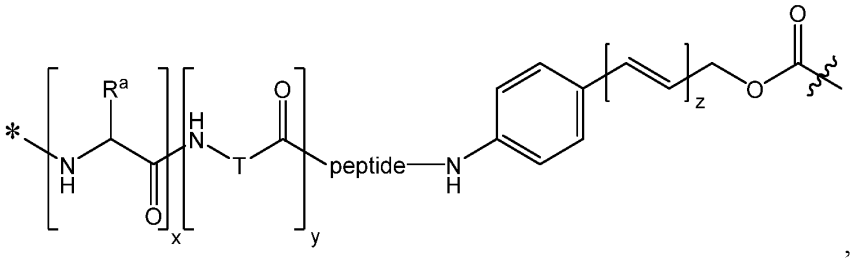
31. The ADC of claim 26, wherein the cleavable linker is an enzyme-cleavable linker.

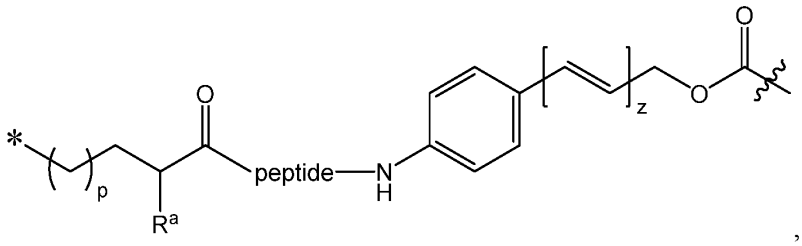
32. The ADC of claim 31, wherein the enzyme-cleavable linker is selected from a polypeptide, tetrapeptide, dipeptide, and a β-glucuronide linker.

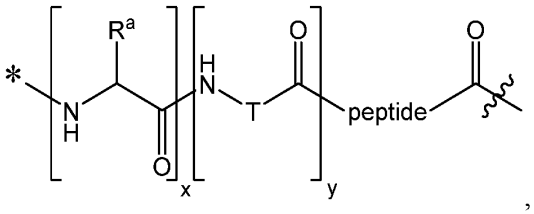
33. The ADC of claim 31 or claim 32, wherein the enzyme cleavable linker is cleavable by a lysosomal enzyme.

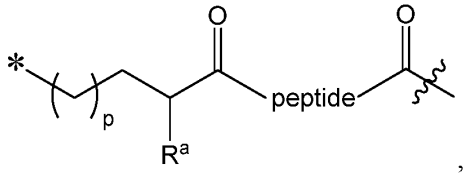
34. The ADC of claim 33, wherein the lysosomal enzyme is a cathepsin.

35. The ADC of claim 34, wherein the linker comprises a segment according to one or more of the structural Formula VIIIa, VIIIb, VIIIc, or VIIId:

(VIIIa) ,

(VIIIb) ,

(VIIIc) ,

(VIIId) ,

or a salt thereof, wherein:

"peptide" represents a peptide cleavable by Cathepsin B;

T represents a polymer comprising one or more ethylene glycol units or an alkylene chain, or combinations thereof;

R^a is selected from hydrogen, C_{1-6}alkyl, sulfonate, and methyl sulfonate;

p is an integer ranging from 0 to 5;

x is 0 or 1;

y is 0 or 1;

z is 0 or 1;

 represents the point of attachment of the linker to D; and

* represents the point of attachment to the remainder of the linker.

36. The ADC of claim 32, wherein the enzyme-cleavable linker is a dipeptide selected from Ala-Ala, Ala-(D)Asp, Ala-Cit, Ala-Lys, Ala-Val, Asn-Cit, Asp-Cit, Asn-Lys, Asn-(D)Lys, Asp-Val, Cit-Ala, Cit-Asn, Cit-Asp, Cit-Cit, Cit-Lys, Cit-Ser, Cit-Val, Glu-Val, PhenylGly-(D)Lys, His-Val, Ile-Cit, Ile-Pro, Ile-Val, Leu-Cit, Lys-Cit, Me3Lys-Pro, Met-Lys, Met-(D)Lys, Phe-Arg, Phe-Cit, Phe-Lys, Pro-(D)Lys, Ser-Cit, Trp-Cit, Val-Ala, Val-(D)Asp, NorVal-(D)Asp, Val-Cit, Val-Glu, and Val-Lys.

37. The ADC of any one of claims 1-36, wherein L comprises one or more self-immolative spacers.

38. The ADC of any one of claims 1-37, wherein L is coupled to Ab via a maleimide group, an activated disulfide, an active ester, a haloformate, an acid halide, an alkyl halide, or a benzyl halide.

39. The ADC of claim 38, wherein L is coupled to Ab via an activated disulfide selected from DSDM, SPDB, and sulfo-SPDB.

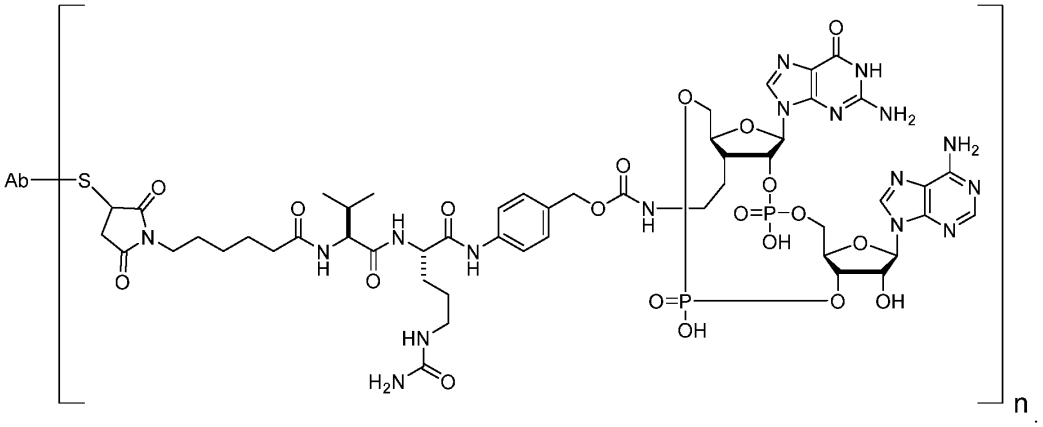
40. The ADC of claim 38, wherein L is coupled to Ab via an active ester selected from an NHS ester and a HOBt ester.

41. The ADC of claim 40, wherein L is coupled to Ab via a maleimidocaproyl (mc) or N-succinimidyl-4-(2-pyridyldithio)butanoate (SPDB) group.

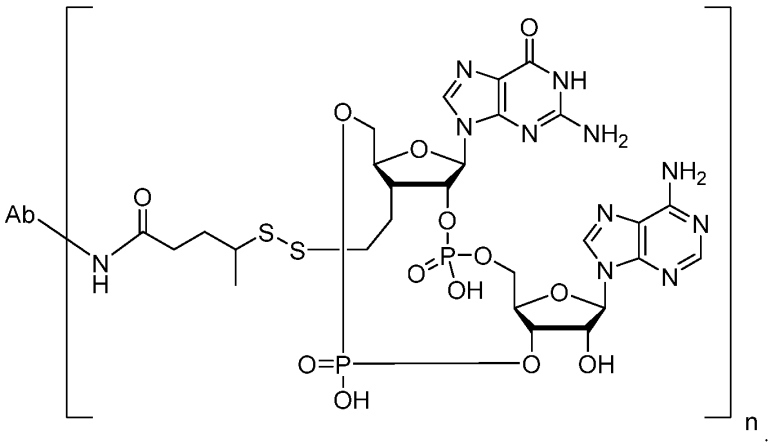
42. The ADC of any one of claims 1-41, having a covalent linkage formed between L and Ab with a thiol group or primary amino group on Ab.

43. The ADC of claim 42, wherein the covalent linkage is a thioether.

44. The ADC of claim 1, wherein the ADC has the following structure:



45. The ADC of claim 1, wherein the ADC has the following structure:



46. The ADC of any one of claims 1-45, wherein n is 1, 2, 3, 4, 5, 6, 7, or 8.

47. The ADC of claim 46, wherein n is 2.

48. The ADC of claim 46, wherein n is 4.

49. The ADC of any one of claims 1-48, wherein Ab is an antibody that binds to PD-L1.

50. The ADC of any one of claims 1-48, wherein Ab is an antibody that binds to an antigen which is a Growth Factor Receptor (GFR).

51. The ADC of claim 50, wherein the GFR is EGFR.

52. The ADC of claim 50, wherein the GFR is ErbB.

53. The ADC of claim 50, wherein the GFR is ErbB2.

54. The ADC of claim 50, wherein the GFR is a HER family receptor.

55. The ADC of any one of claims 1-48, wherein Ab is an antibody that binds to CD47.

56. The ADC of any one of claims 1-48, wherein Ab is an antibody that binds to an antigen preferentially expressed or overexpressed in cancer cells.

57. The ADC of any one of claims 1-48, wherein Ab is an antibody that binds to an antigen derived from a microbe that infects human cells.

58. A pharmaceutical composition comprising the ADC of any one of claims 1-57.

59. A method of stimulating an immune response in a human patient in need thereof, comprising administering an effective amount of the pharmaceutical composition of claim 58 to the patient.

60. A method of treating cancer in a human patient in need thereof, comprising administering an effective amount of the pharmaceutical composition of claim 58 to the patient.

61. The method of claim 59 or 60, wherein the pharmaceutical composition is administered intravenously.

62. The method of claim 59 or 60, wherein the pharmaceutical composition is administered subcutaneously.

63. The method of claim 59 or 60, wherein the pharmaceutical composition is administered intratumorally.

64. The method of any one of claims 59-63, further comprising administering a PD-1 inhibitor to the patient.

65. The method of any one of claims 59-63, further comprising administering a PD-L1 inhibitor to the patient.

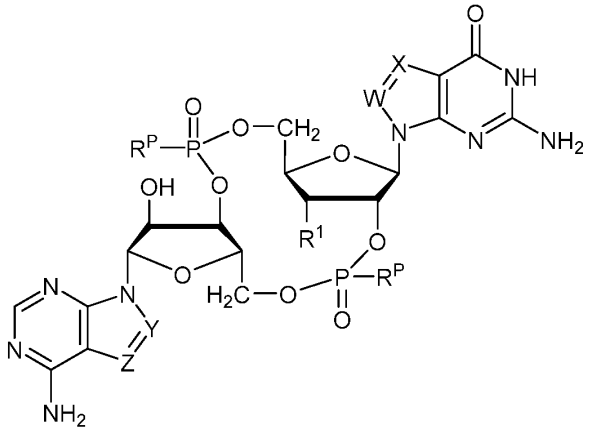
66. The method of any one of claims 59-63, further comprising administering a CTLA-4 inhibitor to the patient.

67. The method of any one of claims 59-63, further comprising administering an additional anti-cancer agent to the patient.

68. The method of any one of claims 59-67, further comprising administering radiation to the patient.

69. The method of any one of claims 59-68, further comprising administering a second CDN to the patient, wherein the second CDN is not conjugated to an antibody.

70. A compound, wherein the compound is of Formula IIk:



Formula IIk

wherein

W, X, Y, and Z are independently CH or N;

R^1 is ethyl substituted with an amino or C_{1-6}alkylamino group;

R^p is, independently for each occurrence, hydroxyl, thiol, C_{1-6}alkyl, borano ($-BH_3^-$), or –NR'R", wherein R' and R" are, independently for each occurrence, hydrogen or C_{1-6}alkyl optionally substituted with one or more groups selected from halogen, thiol, hydroxyl, carboxyl, C_{1-6}alkoxy, C_{1-6}hydroxyalkoxy, -OC(O)C_{1-6}alkyl, -N(H)C(O)C_{1-6}alkyl, -N(C_{1-3}alkyl)C(O)C_{1-6}alkyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, oxo, and azido; or R' and R" on the same nitrogen together form a C_{3-5}heterocyclic ring;

or a pharmaceutically acceptable salt thereof.

71. The compound of claim 70, wherein R^p, independently for each occurrence, is hydroxyl or thiol.

72. The compound of claim 70 or 71, wherein Y and W are both CH.

73. The compound of any one of claims 70-72, wherein X and Z are both N.

74. The compound of any one of claims 70-73, wherein R^1 is ethyl substituted with an amino group.

75. The compound of any one of claims 70-73, wherein R^1 is ethyl substituted with a C_{1-6}alkylamino group.

76. The compound of claim 75, wherein R^1 is ethyl substituted with a methylamino group.

77. The compound of any one of claims 70-76, wherein at least one occurrence of R^P is hydroxyl.

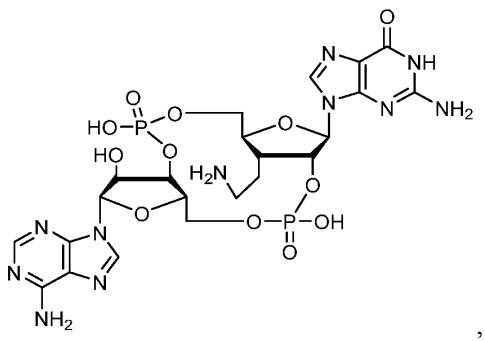
78. The compound of claim 77, wherein both occurrences of R^P are hydroxyl.

79. The compound of claim 77, wherein one occurrence of R^P is hydroxyl and the other is thiol.

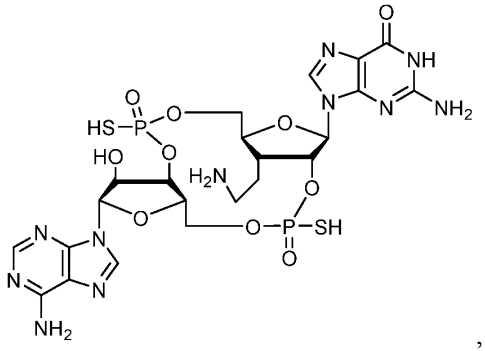
80. The compound of any one of claims 70-76, wherein at least one occurrence of R^P is thiol.

81. The compound of claim 80, wherein both occurrences of R^P are thiol.

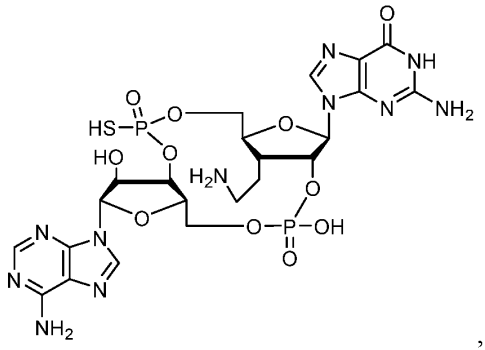
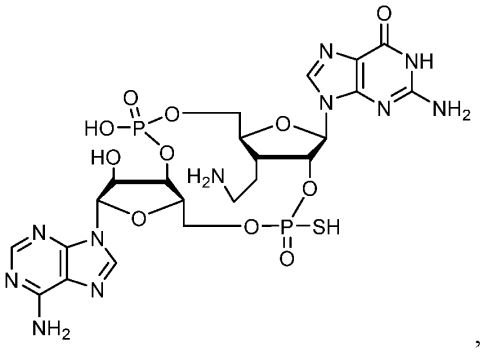
82. The compound of claim 70, wherein the compound is selected from:



,



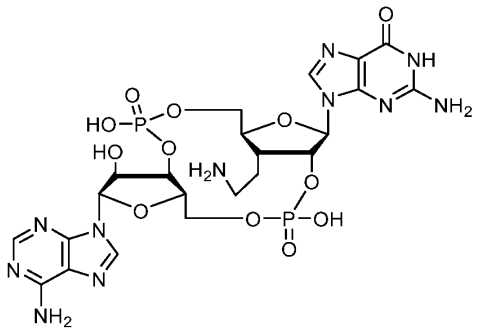
,

, and ,

or a pharmaceutically acceptable salt thereof.

83. The compound of claim 82, wherein the compound is



or a pharmaceutically acceptable salt thereof.

84. A composition comprising a cyclic dinucleotide (CDN) and a base, wherein the CDN is a compound of any one of claims 70-83.

85. The composition of claim 84, wherein the composition consists of the CDN and the base.

86. The composition of claim 84 or 85, wherein the base is an amine base.

87. The composition of claim 86, wherein the amine base is selected from pyridine, piperidine, pyrrolidine, morpholine, lutidine, triethylamine (TEA), and diisopropylethylamine (DIPEA).

88. The composition of claim 87, wherein the amine base is pyridine.

89. A composition comprising:

a cyclic dinucleotide (CDN); and

a linker or a coupling agent, or both a linker and a coupling agent;

wherein the CDN is a compound of any one of claims 70-83 and the coupling agent facilitates coupling of the CDN to the linker.

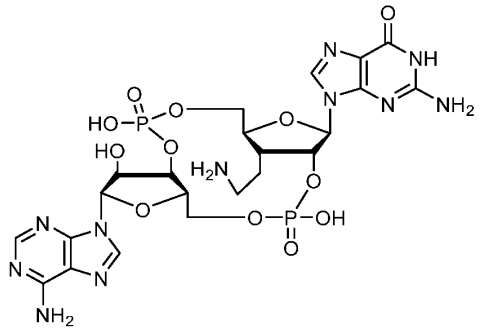
90. The composition of claim 89, wherein the coupling agent is capable of generating an activated ester on the linker.

91. The composition of claim 89 or 90, wherein the composition further comprises an aprotic polar solvent.

92. The composition of claim 91, wherein the aprotic polar solvent is selected from dimethylformamide (DMF), dimethylacetamide (DMA), acetonitrile, or tetrahydrofuran (THF).

93. The composition of any one of claims 84-92, wherein the composition is anhydrous.

94. The composition of any one of claims 84-93, wherein the CDN has the following structure:

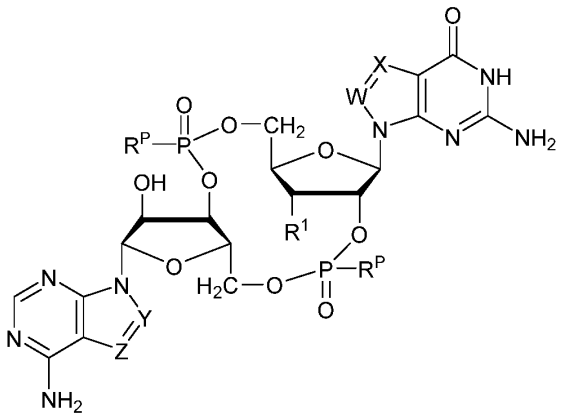


or a pharmaceutically acceptable salt thereof.

95. A compound of the formula L-CDN, wherein

L is a linker that includes a site capable of coupling to a complementary site on an antibody or antigen-binding fragment;

CDN is a cyclic dinucleotide having the structure of Formula IIk:



Formula IIk

wherein

W, X, Y, and Z are independently CH or N;

R^1 is C_{1-6}alkyl substituted with a thiol, amino, or C_{1-6}alkylamino group;

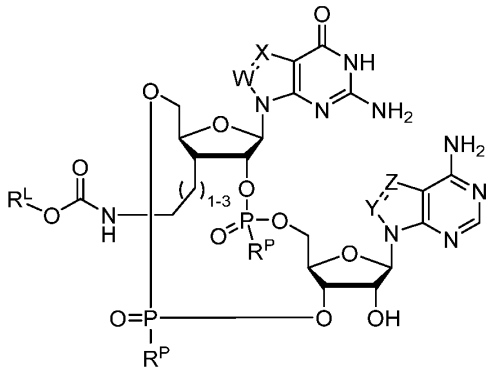
R^p is, independently for each occurrence, hydroxyl, thiol, C_{1-6}alkyl, borano ($-BH_3^-$), or –NR'R", wherein R' and R" are, independently for each occurrence, hydrogen or C_{1-6}alkyl optionally substituted with one or more groups selected from halogen, thiol, hydroxyl, carboxyl, C_{1-6}alkoxy, C_{1-6}hydroxyalkoxy, -OC(O)C_{1-6}alkyl, -N(H)C(O)C_{1-6}alkyl, -N(C_{1-3}alkyl)C(O)C_{1-6}alkyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, oxo, and azido; or R' and R" on the same nitrogen together form a C_{3-5}heterocyclic ring;

or a pharmaceutically acceptable salt thereof; and

CDN is coupled to L at the thiol, amino, or C_{1-6}alkylamino group of R^1.

96. The compound of claim 95, wherein CDN is coupled to L via a thioether, an amide, an ester, a carbamate, a carbonate, a urea, a disulfide, or an ether group.

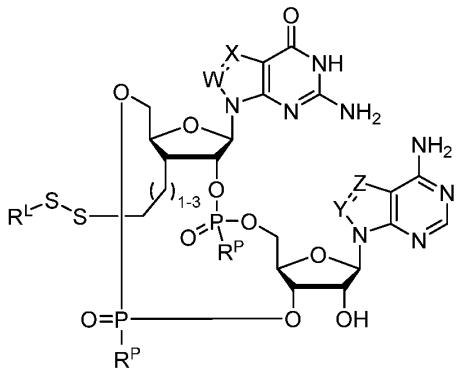
97. The compound of claim 96, wherein the compound has the structure of Formula IXb:



Formula IXb

wherein R^L represents the remainder of the linker L.

98. The compound of claim 96, wherein the compound has the structure of Formula IXf:



Formula IXf

wherein R^L represents the remainder of the linker L.

99. The compound of any one of claims 95-98, wherein R^P, independently for each occurrence, is hydroxyl or thiol.

100. The compound of any one of claims 95-99, wherein Y and W are both CH.

101. The compound of any one of claims 95-100, wherein X and Z are both N.

102. The compound of any one of claims 95-101, wherein R^1 is ethyl substituted with an amino group.

103. The compound of any one of claims 95-101, wherein R^1 is ethyl substituted with a C_{1-6}alkylamino group.

104. The compound of claim 103, wherein R^1 is ethyl substituted with a methylamino group.

105. The compound of any one of claims 95-104, wherein at least one occurrence of R^P is hydroxyl.

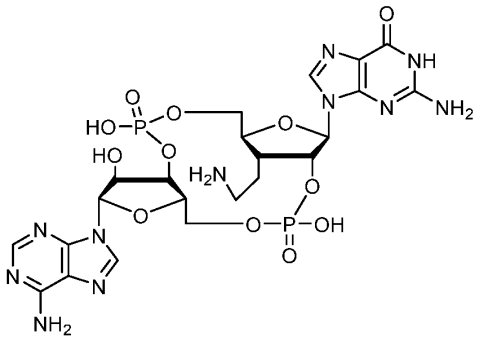
106. The compound of claim 105, wherein both occurrences of R^P are hydroxyl.

107. The compound of claim 105, wherein one occurrence of R^P is hydroxyl and the other is thiol.

108. The compound of any one of claims 95-104, wherein at least one occurrence of R^P is thiol.

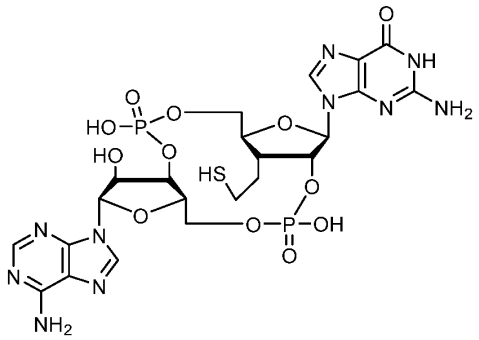
109. The compound of claim 108, wherein both occurrences of R^P are thiol.

110. The compound of claim 95, wherein the CDN has the following structure:



or a pharmaceutically acceptable salt thereof.

111. The compound of claim 95, wherein the CDN has the following structure:



or a pharmaceutically acceptable salt thereof.