CLAIMS

1. ~~A method of inducing CD8+ T cell infiltration into a tumor in a subject in need thereof, wherein the method comprises a step of administering to the subject a~~A radioimmunoconjugate or a pharmaceutical composition thereof for use in inducing infiltration of a CD8+ T cell population into the core of a tumor in a subject in need thereof, wherein the radioimmunoconjugate comprises the following structure:

A-L-B

Formula I-a

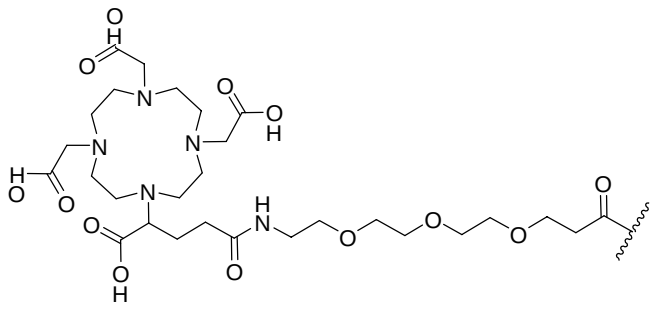
wherein

A is a metal complex of a chelating moiety, wherein the metal complex comprises Actinium-225 (^{225}Ac) or a progeny thereof,

L is a linker, and

B is a targeting moiety capable of binding a first tumor-associated antigen expressed by at least some cells in the tumor;

with the proviso that if A-L- is a metal complex of Compound 1 as shown below, then B is not AVE1642



(Compound 1);

~~wherein said administering of said radioimmunoconjugate results in infiltration of a CD8$^+$ T cell population into the core of the tumor;~~

wherein said CD8$^+$ T cell population comprises CD8+ T cells expressing a T-cell receptor (TCR) specific for a second tumor-associated antigen expressed by at least some cells in the tumor; and

wherein the CD8+ T cell is capable of preferentially killing a cell expressing the second tumor-associated antigen.

2. Use of a radioimmunoconjugate or a pharmaceutical composition thereof in the manufacture of a medicament for inducing infiltration of a CD8+ T cell population into the core of a tumor in a subject in need thereof, wherein the radioimmunoconjugate comprises the following structure:

A-L-B

Formula I-a

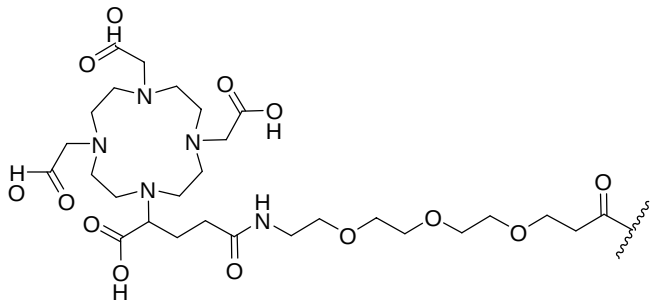
wherein

A is a metal complex of a chelating moiety, wherein the metal complex comprises Actinium-225 (^{225}Ac) or a progeny thereof,

L is a linker, and

B is a targeting moiety capable of binding a first tumor-associated antigen expressed by at least some cells in the tumor;

with the proviso that if A-L- is a metal complex of Compound 1 as shown below, then B is not AVE1642



(Compound 1);

wherein said CD8$^+$ T cell population comprises CD8+ T cells expressing a T-cell receptor (TCR) specific for a second tumor-associated antigen expressed by at least some cells in the tumor; and

wherein the CD8+ T cell is capable of preferentially killing a cell expressing the second tumor-associated antigen.

~~2.~~3. The radioimmunoconjugate or pharmaceutical composition thereof for use ~~method~~ of claim 1 or the use of claim 2, wherein said CD8+ T cell population is detectable in the core of the tumor at a level greater than a reference level.

3. The method of claim 2, wherein said CD8+ T cell population is detectable at a level at least two-fold greater than the reference level.

4. The method of claim 3, wherein said CD8+ T cell population is detectable at a level at least three-fold greater than the reference level.

5. The method of claim 4, wherein said CD8+ T cell population is detectable at a level at least four-fold greater than the reference level.

6. The method of claim 5, wherein said CD8+ T cell population is detectable at a level at least five-fold greater than the reference level.

7. The method of claim 1, wherein said CD8+ T cell population represents at least 5% of cells in the core of the tumor.

8. The method of claim 7, wherein said CD8+ T cell population represents at least 7.5% of cells in the core of the tumor.

9. The method of claim 8, wherein said CD8+ T cell population represents at least 10% of cells in the core of the tumor.

10. The method of claim 9, wherein said CD8+ T cell population represents at least 12.5% of cells in the core of the tumor.

11. The method of claim 10, wherein said CD8+ T cell population represents at least 15% of cells in the core of the tumor.

12. The method of claim 1, wherein said CD8+ T cells represent at least 15% of said CD8+ T cell population.

13. The method of claim 12, wherein said CD8+ T cells represent at least 20% of said CD8+ T cell population.

14. The method of claim 13, wherein said CD8+ T cells represent at least 25% of said CD8+ T cell population.

15. The method of claim 14, wherein said CD8+ T cells represent at least 30% of said CD8+ T cell population.

~~16. The method of claim 15, wherein said CD8+ T cells represent at least 35% of said CD8+ T cell population.~~

~~17. The method of claim 16, wherein said CD8+ T cells represent at least 40% of said CD8+ T cell population.~~

~~18. The method of claim 17, wherein said CD8+ T cells represent at least 45% of said CD8+ T cell population.~~

~~19. The method of claim 18, wherein said CD8+ T cells represent at least 50% of said CD8+ T cell population.~~

~~20. The method of claim 19, wherein said CD8+ T cells represent at least 55% of said CD8+ T cell population.~~

~~21. The method of claim 20, wherein said CD8+ T cells represent at least 60% of said CD8+ T cell population.~~

~~22. The method of claim 21, wherein said CD8+ T cells represent at least 65% of said CD8+ T cell population.~~

~~23. The method of claim 22, wherein said CD8+ T cells represent at least 70% of said CD8+ T cell population.~~

~~24. The method of any one of claims 1-23, wherein said CD8+ T cells are detectable in the subject at least 10 days after the step of administering.~~

~~25. The method of claim 24, wherein said CD8+ T cells are detectable in the subject at least 15 days after the step of administering.~~

~~26. The method of claim 25, wherein said CD8+ T cells are detectable in the subject at least 20 days after the step of administering.~~

~~27. The method of claim 26, wherein said CD8+ T cells are detectable in the subject at least 25 days after the step of administering.~~

~~28. The method of claim 27, wherein said CD8+ T cells are detectable in the subject at least 30 days after the step of administering.~~

29. The method of claim 28, wherein said CD8+ T cells are detectable in the subject at least 40 days after the step of administering.

30.4. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-3 method of any one of claims 1-29, wherein the first tumor-associated antigen is different than the second tumor-associated antigen.

31. The method of claim 30, wherein the second tumor-associated antigen is a neoantigen.

32. The method of any one of claims 1-31, wherein the tumor is a primary tumor.

33. The method of any one of claims 1-31, wherein the tumor is a secondary tumor.

34.5. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-4method of any one of claims 1-33, wherein the tumor is not highly immunogenic.

35.6. The radioimmunoconjugate or pharmaceutical composition thereof for use or the usemethod of claim 345, wherein the tumor is immunologically cold.

36. The method of any one of claims 1-35, wherein the tumor is at least 100 mm3 in volume at the time of administering.

37. The method of claim 36, wherein the tumor is at least 150 mm3 in volume at the time of administering.

38. The method of claim 37, wherein the tumor is at least or about 175 mm3 in volume at the time of administering.

39.7. The radioimmunoconjugate or pharmaceutical composition thereof for use or the usemethod of any one of claims 1-386, wherein the tumor is a solid tumor.

40. The method of claim 39, wherein the solid tumor is a sarcoma.

41. The method of claim 40, wherein the sarcoma is selected from the group consisting of angiosarcoma or hemangioendothelioma, astrocytoma, chondrosarcoma, Ewing's sarcoma, fibrosarcoma, glioma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma (MFH), mesenchymous or mixed mesodermal tumor, mesothelial

~~sarcoma or mesothelioma, myxosarcoma, osteosarcoma, rhabdomyosarcoma, and synovial sarcoma.~~

~~42. The method of claim 41, wherein the sarcoma is osteosarcoma.~~

~~43. The method of claim 39, wherein the solid tumor is a carcinoma.~~

~~44. The method of claim 43, wherein the carcinoma is selected from the group consisting of adenoid cystic carcinoma, adrenocortical carcinoma, bladder cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, gallbladder carcinoma, gastric cancer, head and neck cancer, lung cancer (e.g., small cell lung cancer or non-small cell lung cancer, or adenocarcinoma of the lung), neuroblastoma, neuroendocrine cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, testicular cancer.~~

~~45. The method of claim 44, wherein the carcinoma is bladder cancer.~~

~~46. The method of claim 44, wherein the carcinoma is pancreatic cancer.~~

~~47. The method of claim 44, wherein the carcinoma is breast cancer.~~

~~48. The method of claim 44, wherein the carcinoma is head and neck cancer.~~

~~49. The method of claim 44, wherein the carcinoma is liver cancer.~~

~~50. The method of claim 44, wherein the carcinoma is lung cancer.~~

~~51. The method of claim 44, wherein the carcinoma is a brain cancer.~~

~~52. The method of claim 44, wherein the carcinoma is neuroblastoma.~~

~~53. The method of claim 44, wherein the carcinoma is melanoma.~~

~~54.~~8. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use~~method~~ of any one of claims 1-~~38~~7, wherein the tumor is a liquid tumor.

~~55.~~9. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use~~method~~ of any one of claims 1-~~54~~8, wherein said ~~step of administering~~use results in inhibition of cell proliferation in the core of the tumor.

~~56.~~10. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use~~method~~ of any one of claims 1-~~55~~9, wherein said ~~step of administering~~use results in slowing or inhibiting progression of the tumor.

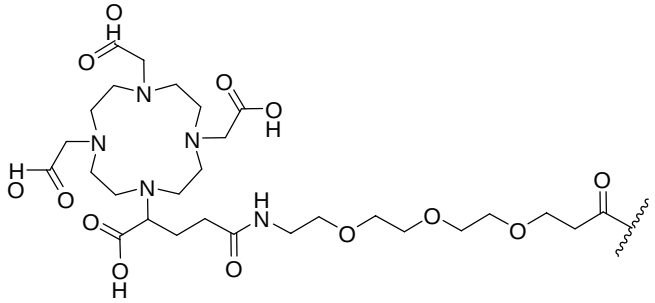
~~57.~~11. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use~~method~~ of claim ~~56~~10, wherein said ~~step of administering~~use results in regression of the tumor.

~~58. The method of claim 57, wherein said step of administering results in complete regression of the tumor.~~

~~59. The method of any one of claims 1-58, wherein said step of administering prevents or inhibits metastasis of tumor cells.~~

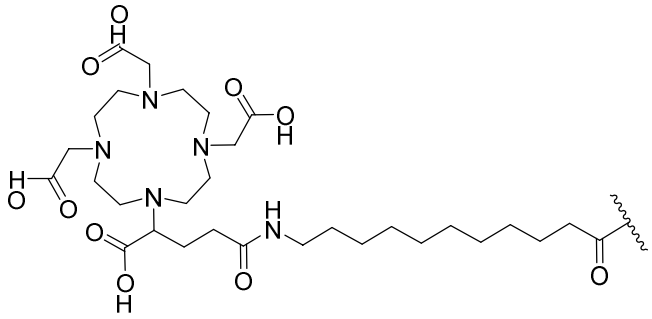
~~60.~~12. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use~~method~~ of any one of claims 1-~~59~~11, wherein A-L- is a metal complex of a compound selected from the group consisting of

(i)

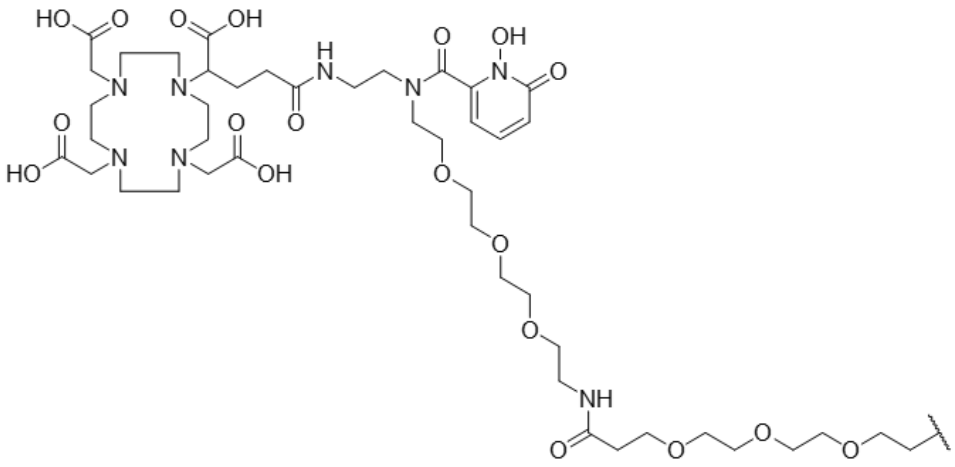


(Compound 1),

(ii)

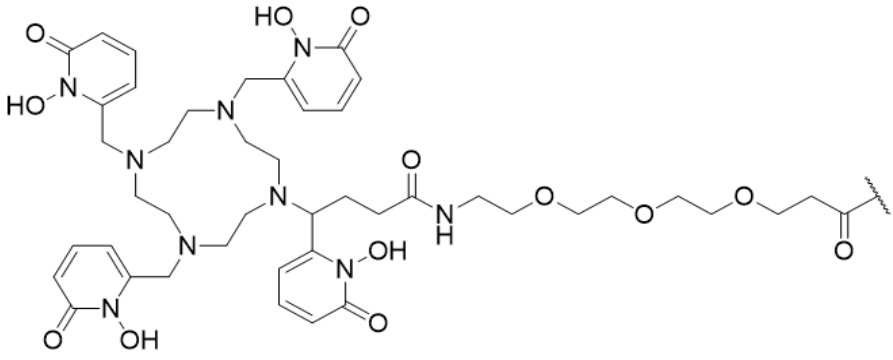


(Compound 2),



(iii)

(Compound 3), and



(iv)

(Compound 4).

~~61.~~13. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use~~method~~ of any one of claims 1-~~60~~12, wherein L has the structure -L^1-$(L^2)_n$-, as shown within Formula I-b:

$$A\text{-}L^1\text{-}(L^2)_n\text{-}B$$

Formula I-b

wherein

A is a metal complex of chelating moiety, wherein the metal complex comprises a Actinium-225 (^{225}Ac) or a progeny thereof;

B is a targeting moiety;

L^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted aryl or heteroaryl;

n is 1-5; and

each L^2, independently, has the structure:

$$(-X^1\text{-}L^3\text{-}Z^1\text{-})$$

Formula III

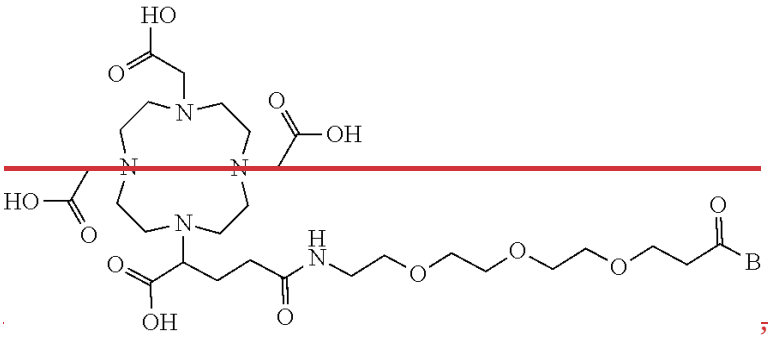
wherein

X^1 is C=O(NR^1), C=S(NR^1), OC=O(NR^1), NR^1C=O(O), NR^1C=O(NR^1), -CH_2PhC=O(NR^1), -CH_2Ph(NH)C=S(NR^1) , O, or NR^1; and each R^1 independently is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted aryl or heteroaryl, in which C_1-C_6 alkyl can be substituted by oxo (=O), heteroaryl, or a combination thereof;

L^3 is optionally substituted C_1-C_{50} alkyl or optionally substituted C_1-C_{50} heteroalkyl; and

Z^1 is CH_2, C=O, C=S, OC=O, NR^1C=O, or NR^1 , wherein R^1 is a hydrogen or optionally substituted C_1-C_6 alkyl or pyrrolidine-2,5-dione.

~~62. The method of claim 61, wherein the radioimmunoconjugate comprises the following structure:~~



~~wherein B is the targeting moiety.~~

~~63.~~14. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use~~method~~ of any one of claims 1-~~62~~13, wherein the targeting moiety comprises a polypeptide.

~~64.~~15. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of claim 14~~method of any one of claims 1-63~~, wherein the targeting moiety comprises an antibody or an antigen-binding fragment thereof.

65.16. The radioimmunoconjugate or pharmaceutical composition thereof for use or the usemethod of any one of claims 1-6415, wherein the targeting moiety has a molecular weight of at least 100 kDa.

66. The method of claim 65, wherein the targeting moiety has a molecular weight of at least 125 kDa.

67. The method of claim 66, wherein the targeting moiety has a molecular weight of at least 150 kDa.

68.17. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use method of any one of claims 1-6216, wherein the targeting moiety is a small molecule.

69. The method of any one of claims 1-68, wherein the first tumor-associated antigen is selected from the group consisting of Insulin-like Growth Factor 1 Receptor (IGF-1R), tumor epithelial marker-1 (TEM-1), and Fibroblast Growth Factor Receptor 3 (FGFR3).

70.18. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use method of any one of claims 1-6917, wherein the subject is a mammal.

71. The method of claim 70, wherein the subject is a human.

72.19. The radioimmunoconjugate or pharmaceutical composition thereof for use or the usemethod of any one of claims 1-7118, wherein the subject is in need of treatment or prevention of cancer.

73. The method of claim 72, wherein the subject is diagnosed as having cancer.

74. The method of any one of claims 1-73, wherein the subject is in need of treatment of a refractory cancer.

75.20. The radioimmunoconjugate or pharmaceutical composition thereof for use or the usemethod of any one of claims 1-7419, wherein the usestep of administering comprises systemic administration of the radioimmunoconjugate.

~~76. The method of claim 75, wherein systemic administration comprises parenteral administration.~~

~~77. The method of claim 76, wherein parenteral administration comprises intravenous administration.~~

~~78. The method of claim 76, wherein parenteral administration comprises intraarterial administration.~~

~~79. The method of claim 76, wherein parenteral administration comprises intraperitoneal administration.~~

~~80. The method of claim 76, wherein parenteral administration comprises subcutaneous administration.~~

~~81. The method of claim 76, wherein parenteral administration comprises intradermal administration.~~

~~82. The method of claim 75, wherein systemic administration comprises enteric administration.~~

~~83. The method of claim 82, wherein enteric administration comprises trans-gastroenteric administration.~~

~~84. The method of claim 82, wherein enteric administration comprises oral administration.~~

~~85.~~21. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use~~method~~ of any one of claims 1-~~84~~20, wherein the ~~step of administering~~use comprises local administration of the radioimmunoconjugate.

~~86. The method of claim 85, wherein local administration comprises peritumoral injection.~~

~~87. The method of claim 85, wherein local administration comprises intratumoral injection.~~

~~88. The method of any one of claims 1-87, wherein the step of administering comprises contacting, *ex vivo*, the radioimmunoconjugate with a body fluid of said subject, wherein said body fluid contains at least one cancer cell.~~

~~89. The method of any one of claims 1-88, wherein the radioimmunoconjugate is not administered in combination with another cytotoxic agent.~~

~~90.~~22. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use~~method~~ of any one of claims 1-~~89~~21, ~~said method further comprising administering to the subject~~wherein an additional therapeutic agent is to be administered to the subject after the administration~~step~~ of ~~administering~~ the radioimmunoconjugate.

~~91. The method of claim 90, wherein the additional therapeutic agent is a non-cytotoxic agent.~~

~~92.~~23. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use~~method~~ of claim 22~~90 or 91~~, wherein the radioimmunoconjugate or the additional therapeutic agent is to be administered in a lower effective dose.

~~93. The method of claim 90, 91, or 92 wherein the additional therapeutic agent is administered in a lower effective dose.~~