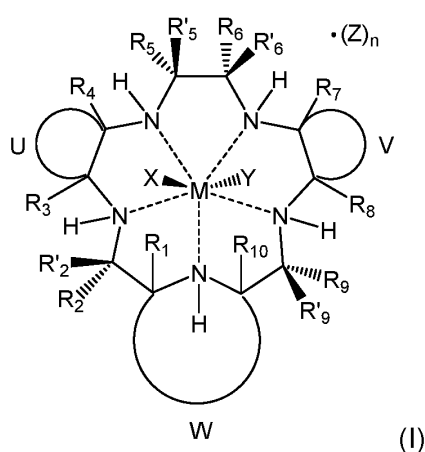


WHAT IS CLAIMED IS:

1. A method of treating a cancer in a mammalian subject afflicted with the cancer, the method comprising:

- 5 administering to the subject an immune checkpoint inhibitor;
 administering to the subject a pentaaza macrocyclic ring complex corresponding to the formula (I) below, prior to, concomitantly with, or after administration of the immune checkpoint inhibitor, to increase the response of the cancer to the immune checkpoint inhibitor:

10



wherein

M is Mn^{2+} or Mn^{3+} ;

- 15 $R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9,$ and R_{10} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting of $-OR_{11}, -NR_{11}R_{12}, -COR_{11}, -CO_2R_{11}, -CONR_{11}R_{12}, -SR_{11}, -SOR_{11}, -SO_2R_{11}, -SO_2NR_{11}R_{12}, -N(OR_{11})(R_{12}), -P(O)(OR_{11})(OR_{12}), -P(O)(OR_{11})(R_{12}),$ and $-OP(O)(OR_{11})(OR_{12}),$ wherein R_{11} and R_{12} are independently hydrogen or alkyl;

- 20 U, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;

V, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;

5 W, together with the nitrogen of the macrocycle and the carbon atoms of the macrocycle to which it is attached, forms an aromatic or alicyclic, substituted or unsubstituted, saturated, partially saturated or unsaturated nitrogen-containing fused heterocycle having 2 to 20 ring carbon atoms, provided that when W is a fused aromatic heterocycle the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and R₁ and R₁₀ attached to the carbon atoms which are both part of
10 the heterocycle and the macrocycle are absent;

X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof;

Z is a counterion;

n is an integer from 0 to 3; and

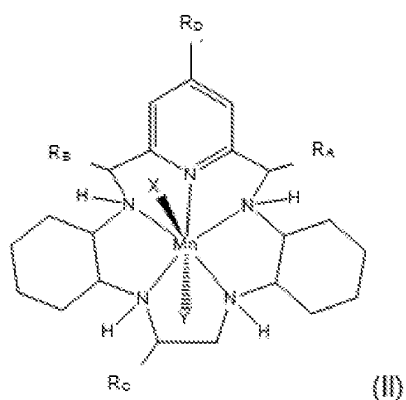
15 the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.

2. The method according to claim 1, wherein R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R₆, R'₆, R₇, R₈, R₉, R'₉, and R₁₀ are each hydrogen.
20

3. The method according to claim 1 or 2, wherein W is an unsubstituted pyridine moiety.

4. The method according to any preceding claim, wherein U and V are
25 transcyclohexanyl fused rings.

5. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is represented by formula (II):

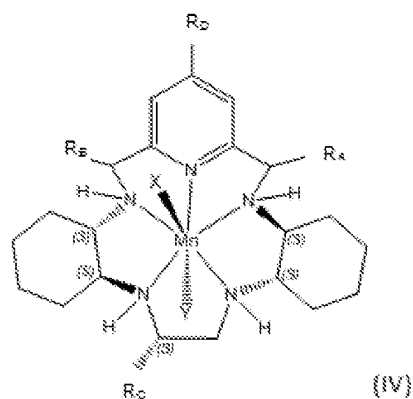
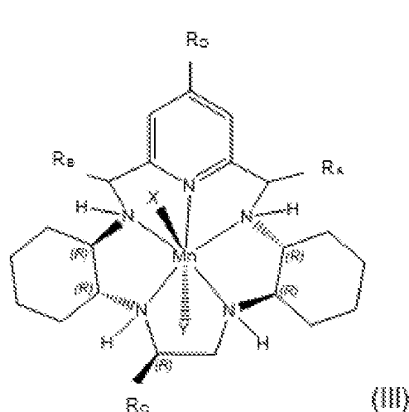


wherein

- 5 X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and
- R_A , R_B , R_C , and R_D are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected
- 10 from the group consisting of $-OR_{11}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{11}$, $-CONR_{11}R_{12}$, $-SR_{11}$, $-SOR_{11}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$, $-N(OR_{11})(R_{12})$, $-P(O)(OR_{11})(OR_{12})$, $-P(O)(OR_{11})(R_{12})$, and $-OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or alkyl.

15

6. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is represented by formula (III) or formula (IV):



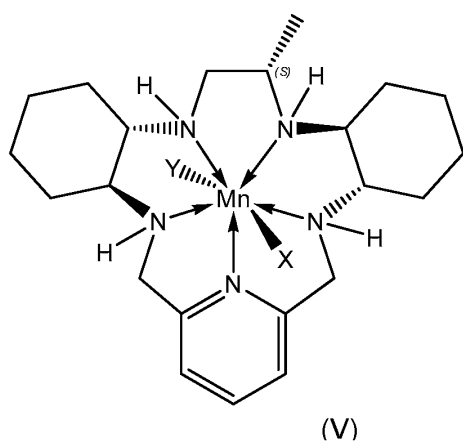
wherein

X and Y represent suitable ligands which are derived from any monodentate or
 5 polydentate coordinating ligand or ligand system or the corresponding anion
 thereof; and

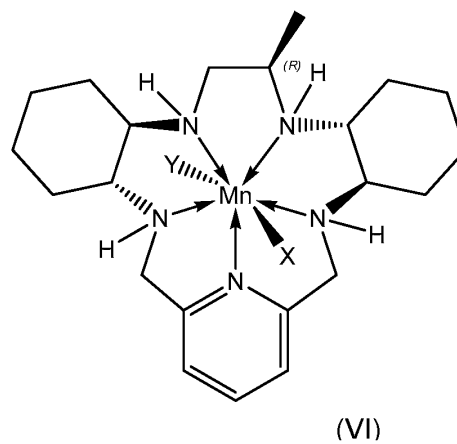
R_A , R_B , R_C , and R_D are independently hydrogen, hydrocarbyl, substituted
 hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected
 from the group consisting

10 of $-OR_{11}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{11}$, $-CONR_{11}R_{12}$, $-SR_{11}$, $-SOR_{11}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$, $-N(OR_{11})(R_{12})$, $-P(O)(OR_{11})(OR_{12})$, $-P(O)(OR_{11})(R_{12})$,
 and $-OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or
 alkyl.

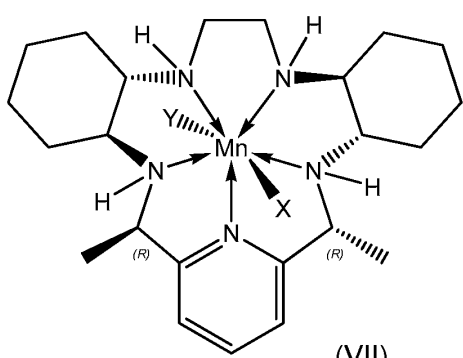
15 7. The method according to any preceding claim, wherein the pentaaza
 macrocyclic ring complex is a compound represented by a formula selected from the
 group consisting of formulae (V)-(XVI):



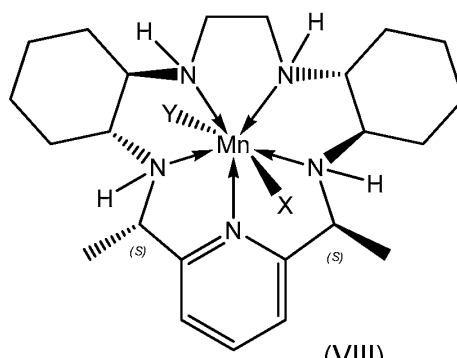
(V)



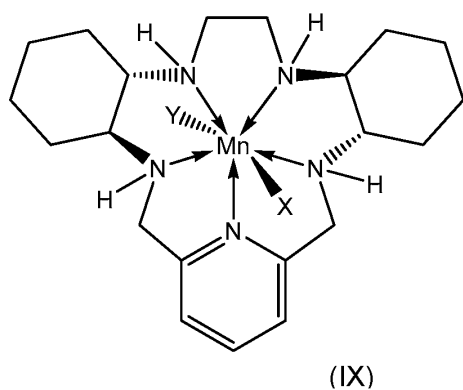
(VI)



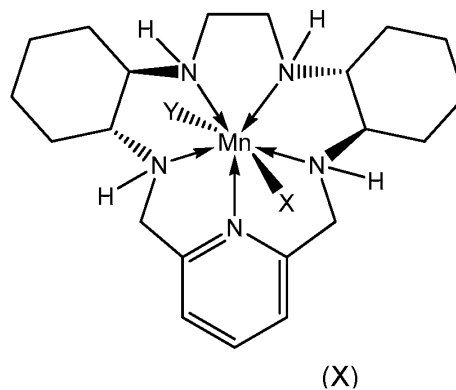
(VII)



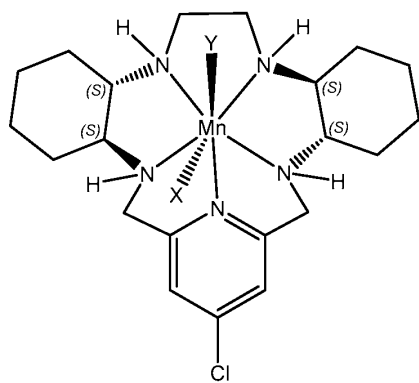
(VIII)



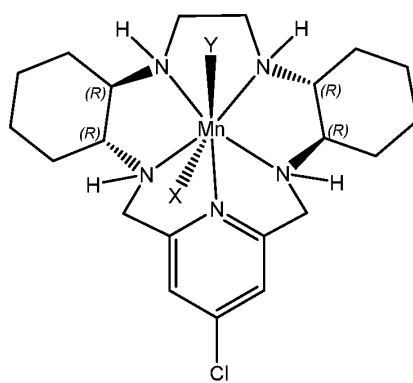
(IX)



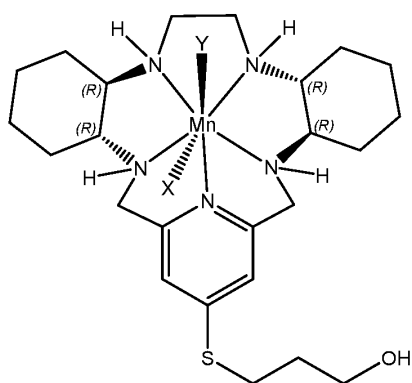
(X)



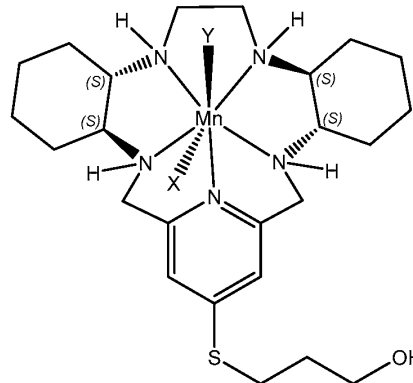
(XI)



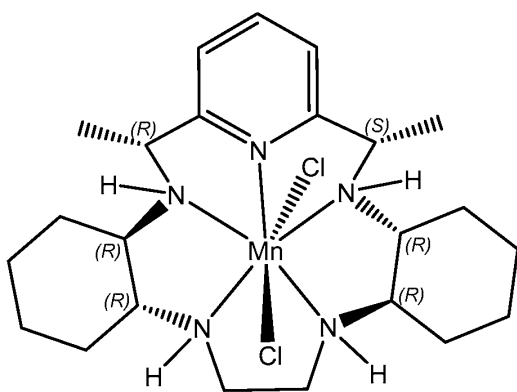
(XII)



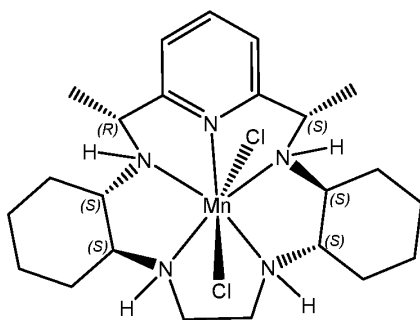
(XIII)



(XIV)



(XV)



(XVI)

5

8. The method according to any preceding claim, wherein X and Y are independently selected from substituted or unsubstituted moieties of the group consisting of halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen, peroxy, hydroperoxy, alkylperoxy, arylperoxy, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid, aryl carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate, aryl thiocarbamate, alkylaryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate,

tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins, or the corresponding anions thereof;

- or X and Y correspond to $-O-C(O)-X_1$, where each X_1 is $-C(X_2)(X_3)(X_4)$, and
- 5 each X_1 is independently substituted or unsubstituted phenyl or $-C(-X_2)(-X_3)(-X_4)$;
- each X_2 is independently substituted or unsubstituted phenyl, methyl, ethyl or propyl;
- each X_3 is independently hydrogen, hydroxyl, methyl, ethyl, propyl, amino,
- 10 $-X_5C(=O)R_{13}$ where X_5 is NH or O, and R_{13} is C1-C18 alkyl, substituted or unsubstituted aryl or C1-C18 aralkyl, or $-OR_{14}$, where R_{14} is C1-C18 alkyl, substituted or unsubstituted aryl or C1-C18 aralkyl, or together with X_4 is $(=O)$; and
- each X_4 is independently hydrogen or together with X_3 is $(=O)$;
- 15 or X and Y are independently selected from the group consisting of charge-neutralizing anions which are derived from any monodentate or polydentate coordinating ligand and a ligand system and the corresponding anion thereof;
- or X and Y are independently attached to one or more of $R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9$, and R_{10} .

20

9. The method according to any preceding claim, wherein X and Y are independently selected from the group consisting of fluoro, chloro, bromo, and iodo anions.

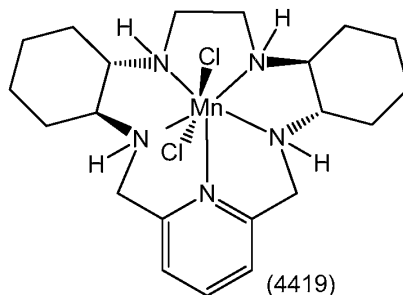
25

10. The method according to any one of claims 1-8, wherein X and Y are independently selected from the group consisting of alkyl carboxylates, aryl carboxylates and arylalkyl carboxylates.

30

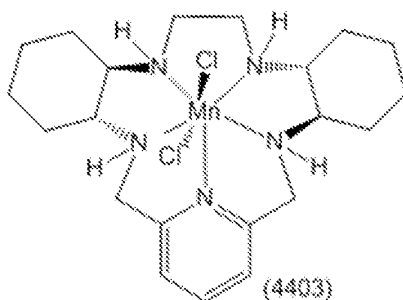
11. The method according to any one of claims 1-8, wherein X and Y are independently amino acids.

12. The method according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



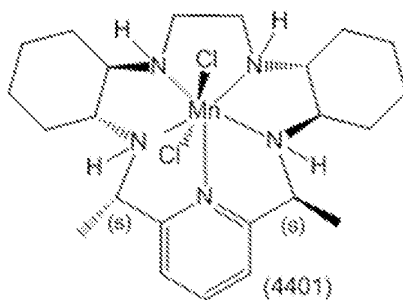
5

13. The method according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



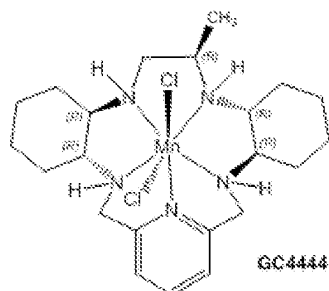
10

14. The method according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:

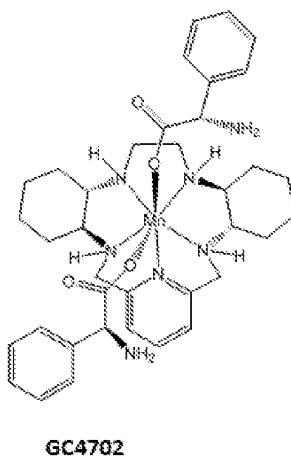


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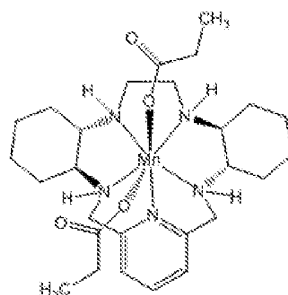
15. The method according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is represented by the formula:



5 16. The method according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is represented by the formula:



10 17. The method according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is represented by the formula:



GC4711

18. The method according to any one of claims 1-8, wherein initial administration of the pentaaza macrocyclic ring complex in a course of therapy is administered a predetermined period of time after initial administration of the immune checkpoint inhibitor.

19. The method according to claim 18, wherein initial administration of the pentaaza macrocyclic ring complex in the course of therapy is no less than 3 days after
10 initial administration of the immune checkpoint inhibitor.

20. The method according to claim 19, wherein initial administration of the pentaaza macrocyclic ring complex in the course of therapy is no less than 6 days after initial administration of the immune checkpoint inhibitor.

21. The method according to claim 19, wherein initial administration of the pentaaza macrocyclic ring complex in the course of therapy is in a range of from 3 days to 9 weeks after initial administration of the immune checkpoint inhibitor.

20 22. The method according to any preceding claim, wherein initial administration of the pentaaza macrocyclic ring complex in the course of therapy follows two doses of the immune checkpoint inhibitor.

23. The method according to claim 22, wherein initial administration of the pentaaza macrocyclic ring complex in the course of therapy follows three doses of the immune checkpoint inhibitor.

5 24 The method according to claim 23, wherein initial administration of the pentaaza macrocyclic ring complex in the course of therapy follows four doses of the immune checkpoint inhibitor.

10 25. The method according to claim 24, wherein initial administration of the pentaaza macrocyclic ring complex in the course of therapy follows five doses of the immune checkpoint inhibitor.

15 26. The method according to any preceding claim, wherein doses of the pentaaza macrocyclic ring complex provided in a course of cancer therapy are provided on separate days from any dose of the immune checkpoint inhibitor.

20 27. The method according to any preceding claim, comprising administering the immune checkpoint inhibitor and pentaaza macrocyclic ring complex to a subject that is not receiving radiation therapy.

25 28. The method according to any preceding claim, wherein the checkpoint inhibitor interacts with one or more of cytotoxic T-lymphocyte antigen 4 (CTLA4), programmed death 1 (PD-1), programmed death ligand 1 (PDL-1), PDL-2, lymphocyte activation genes-3 (LAG3), B7 homolog 3 (B7-H3), B7 homolog 4 (B7-H4), indoleamine (2,3)-dioxygenase (IDO), adenosine A2a receptor (A2AR), neuritin, B- and T-lymphocyte attenuator (BTLA), killer immunoglobulin-like receptors (KIR), T cell immunoglobulin and mucin domain-containing protein 3 (TIME-3), inducible T cell costimulator (ICOS), CD27, CD28, CD40, CD137, CD160, CD244, HVEM, GAL9, VISTA, 2B4, CGEN-15049, CHK 1, CHK 2, GITR, CD47 and combinations thereof.

30 29. The method according to any preceding claim, wherein the checkpoint inhibitor comprises one or more of a small molecular inhibitor, an antibody, an antigen binding fragment, and an Ig fusion protein.

30. The method according to any preceding claim, wherein the checkpoint inhibitor is selected from the group consisting of ipilimumab, nivolumab, pembrolizumab, pidilizumab, areluman, tremelimumab, atezolizumab, AMP-224, MPDL3280A, MDX-1105, MDX-1106, MEDI-4736, IMP321, INCB024360, NLG-919, indoximod, AUNP 12, galiximab, avelumab, varlilumab, mogamulizumab, CP-870,893, MEDI-6469, IPH2101, urelumab, lirilumab, BMS-986016, MGA271, IMP321, BMS-936559, MSB0010718C, anti-OX40, MK-3475, CT-011, BY55, AMP224, and BGB-A317.

31. The method according to any preceding claim, wherein the checkpoint inhibitor is at least one of an anti-CTLA4 antibody, an anti-PD-1 antibody and an anti-PDL-1 antibody.

32. The method according to any preceding claim, further comprising administering one or more of adoptive T-cell transfer therapy and a cancer vaccine to the subject, either prior to, concomitantly with, or after administration of one or more of the checkpoint inhibitor and pentaaza macrocyclic ring complex.

33. The method according to any preceding claim, wherein the cancer is selected from the group consisting of breast cancer, non-small-cell lung cancer, melanoma, renal cell carcinoma, urothelial carcinoma, bladder cancer, pancreatic cancer, head and neck cancers, colorectal cancer, prostate cancer, brain cancer, spindle cell carcinoma, and oral squamous cell carcinoma.

34. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered to the subject in a dose in a range of from 0.2 mg/kg to 40 mg/kg.

35. The method according to claim 34, wherein the pentaaza macrocyclic ring complex is administered to the subject in a dose in a range of from 0.2 mg/kg to 24 mg/kg.

36. The method according to claim 35, wherein the pentaaza macrocyclic ring complex is administered to the subject in a dose in a range of from 0.2 mg/kg to 10 mg/kg.

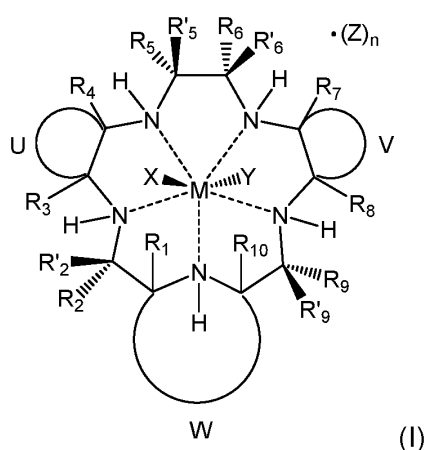
37. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered via at least one of parenteral route and oral route.

5

38. The method according to claim 37, wherein the pentaaza macrocyclic ring complex is administered intraperitoneally or intravenously.

39. A method of treating a cancer in a mammalian subject afflicted with the cancer, the method comprising:
 administering to the subject an adoptive T-cell transfer therapy;
 administering to the subject a pentaaza macrocyclic ring complex corresponding to the formula (I) below, prior to, concomitantly with, or after the adoptive T-cell transfer therapy, to increase the response of the cancer to the adoptive T-cell transfer therapy,

15



wherein

M is Mn^{2+} or Mn^{3+} ;

20 R_1 , R_2 , R'_2 , R_3 , R_4 , R_5 , R'_5 , R_6 , R'_6 , R_7 , R_8 , R_9 , R'_9 , and R_{10} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting of $-OR_{11}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{11}$, $-CONR_{11}R_{12}$, $-SR_{11}$, $-SOR_{11}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$

12, $-N(OR_{11})(R_{12})$, $-P(O)(OR_{11})(OR_{12})$, $-P(O)(OR_{11})(R_{12})$, and $-OP(O)(OR_{11})(OR_{12})$,
wherein R_{11} and R_{12} are independently hydrogen or alkyl;

U, together with the adjacent carbon atoms of the macrocycle, forms a fused
substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or
5 heterocycle having 3 to 20 ring carbon atoms;

V, together with the adjacent carbon atoms of the macrocycle, forms a fused
substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or
heterocycle having 3 to 20 ring carbon atoms;

W, together with the nitrogen of the macrocycle and the carbon atoms of the
10 macrocycle to which it is attached, forms an aromatic or alicyclic, substituted or
unsubstituted, saturated, partially saturated or unsaturated nitrogen-containing fused
heterocycle having 2 to 20 ring carbon atoms, provided that when W is a fused aromatic
heterocycle the hydrogen attached to the nitrogen which is both part of the heterocycle
and the macrocycle and R_1 and R_{10} attached to the carbon atoms which are both part of
15 the heterocycle and the macrocycle are absent;

X and Y represent suitable ligands which are derived from any monodentate or
polydentate coordinating ligand or ligand system or the corresponding anion thereof;

Z is a counterion;

n is an integer from 0 to 3; and

20 the dashed lines represent coordinating bonds between the nitrogen atoms of the
macrocycle and the transition metal, manganese.

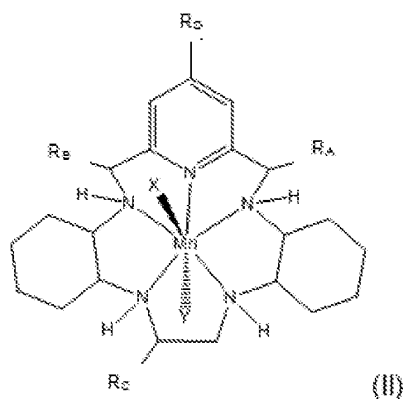
40. The method according to claim 39, wherein R_1 , R_2 , R'_2 , R_3 , R_4 , R_5 , R'_5 , R_6 ,
 R'_6 , R_7 , R_8 , R_9 , R'_9 , and R_{10} are each hydrogen.

25

41. The method according to claim 39 or 40, wherein W is an unsubstituted
pyridine moiety.

42. The method according to any of claims 39-41, wherein U and V are
30 transcyclohexanyl fused rings.

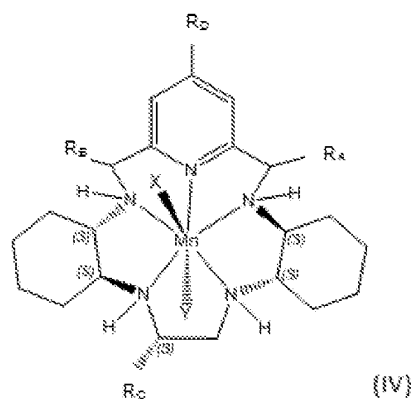
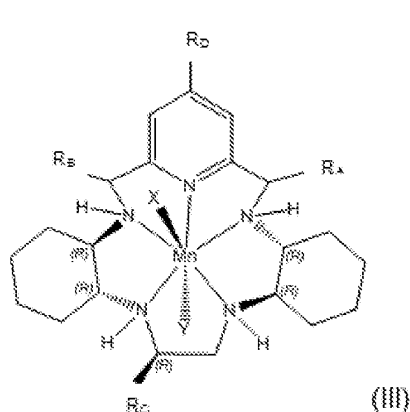
43. The method according to any of claims 39-42, wherein the pentaaza macrocyclic ring complex is represented by formula (II):



wherein

- 5 X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and
- R_A , R_B , R_C , and R_D are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting
- 10 of $-OR_{11}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{11}$, $-CONR_{11}R_{12}$, $-SR_{11}$, $-SOR_{11}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$, $-N(OR_{11})(R_{12})$, $-P(O)(OR_{11})(OR_{12})$, $-P(O)(OR_{11})(R_{12})$, and $-OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or alkyl.

- 15 44. The method according to any of claims 39-43, wherein the pentaaza macrocyclic ring complex is represented by formula (III) or formula (IV):



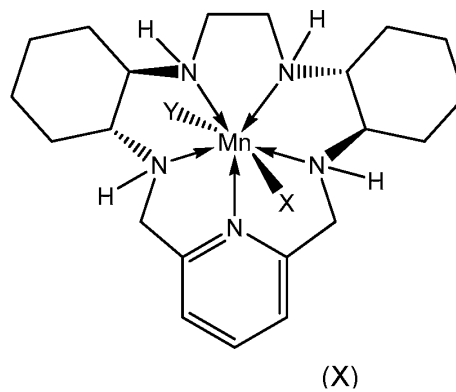
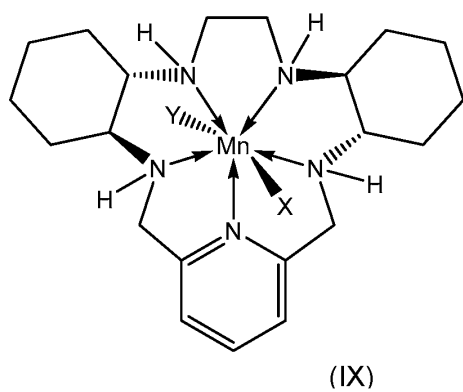
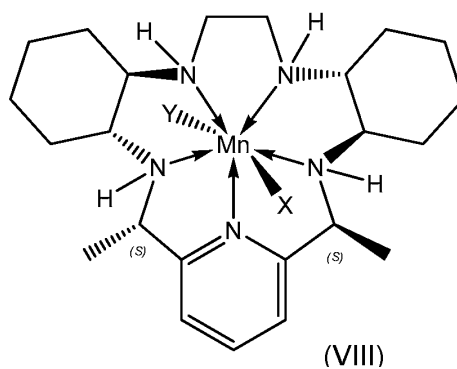
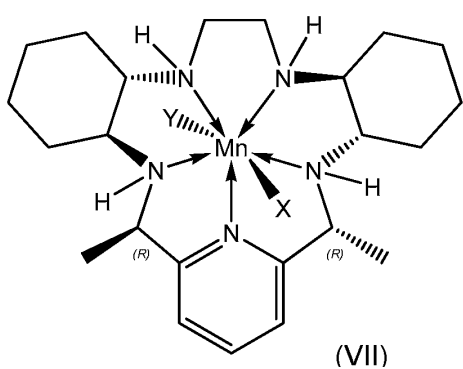
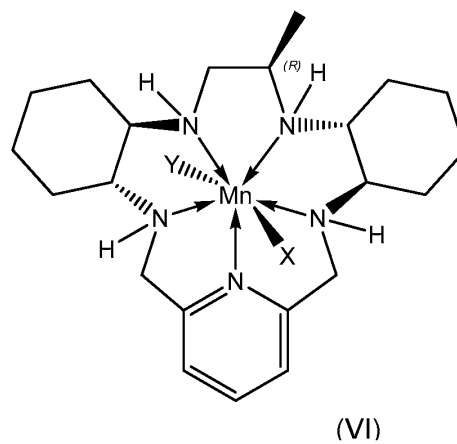
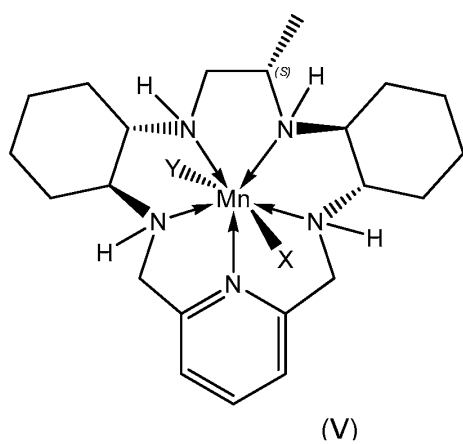
wherein

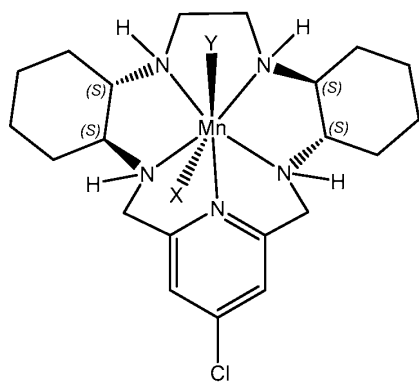
X and Y represent suitable ligands which are derived from any monodentate or
 5 polydentate coordinating ligand or ligand system or the corresponding anion
 thereof; and

R_A , R_B , R_C , and R_D are independently hydrogen, hydrocarbyl, substituted
 hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected
 from the group consisting

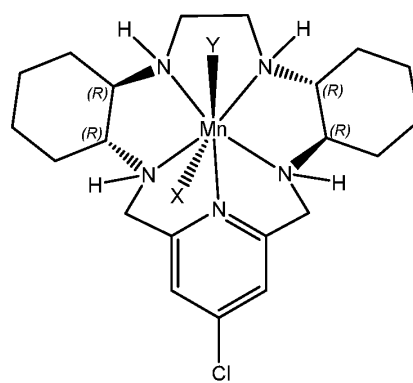
10 of $-OR_{11}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{11}$, $-CONR_{11}R_{12}$, $-SR_{11}$, $-SOR_{11}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$, $-N(OR_{11})(R_{12})$, $-P(O)(OR_{11})(OR_{12})$, $-P(O)(OR_{11})(R_{12})$,
 and $-OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or
 alkyl.

15 45. The method according to any of claims 39-44, wherein the pentaaza
 macrocyclic ring complex is a compound represented by a formula selected from the
 group consisting of formulae (V)-(XVI):

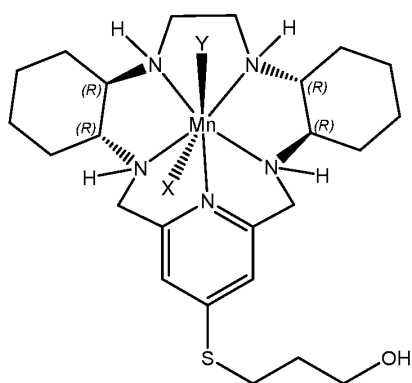




(XI)

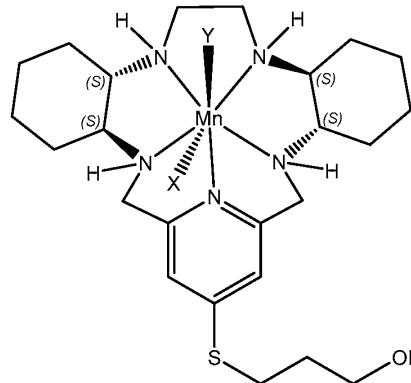


(XII)

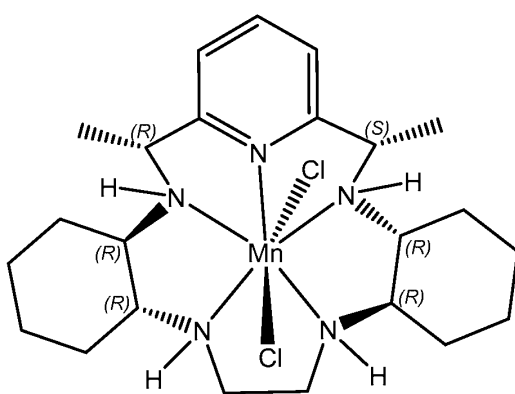


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(XIII)



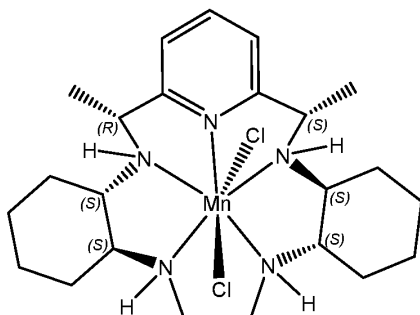
(XIV)



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(XV)



(XVI)

- 5 46. The method according to any of claims 39-45, wherein X and Y are independently selected from substituted or unsubstituted moieties of the group consisting of halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen, peroxy, hydroperoxy, alkylperoxy, arylperoxy, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, 10 nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid, 15 aryl carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, 20 thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate, aryl thiocarbamate, alkylaryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, 25 alkylaryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate,

saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins, or the corresponding anions thereof;

or X and Y correspond to $-O-C(O)-X_1$, where each X_1 is $-C(X_2)(X_3)(X_4)$, and

each X_1 is independently substituted or unsubstituted phenyl or $-C(-X_2)(-X_3)(-X_4)$;

each X_2 is independently substituted or unsubstituted phenyl, methyl, ethyl or propyl;

each X_3 is independently hydrogen, hydroxyl, methyl, ethyl, propyl, amino, $-X_5C(=O)R_{13}$ where X_5 is NH or O, and R_{13} is C1-C18 alkyl, substituted or unsubstituted aryl or C1-C18 aralkyl, or $-OR_{14}$, where R_{14} is C1-C18 alkyl, substituted or unsubstituted aryl or C1-C18 aralkyl, or together with X_4 is $(=O)$; and

each X_4 is independently hydrogen or together with X_3 is $(=O)$;

or X and Y are independently selected from the group consisting of

charge-neutralizing anions which are derived from any monodentate or polydentate coordinating ligand and a ligand system and the corresponding anion thereof;

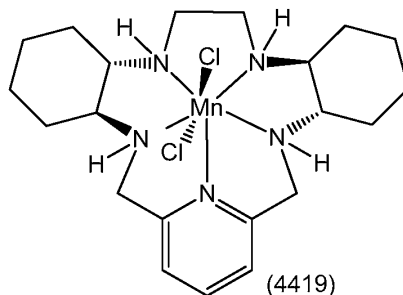
or X and Y are independently attached to one or more of R_1 , R_2 , R'_2 , R_3 , R_4 , R_5 , R'_5 , R_6 , R'_6 , R_7 , R_8 , R_9 , R'_9 , and R_{10} .

47. The method according to any of claims 39-46, wherein X and Y are independently selected from the group consisting of fluoro, chloro, bromo, and iodo anions.

48. The method according to any one of claims 39-46, wherein X and Y are independently selected from the group consisting of alkyl carboxylates, aryl carboxylates and arylalkyl carboxylates.

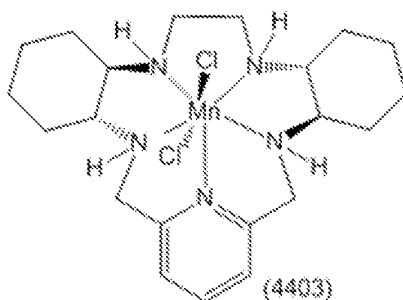
49. The method according to any one of claims 39-46, wherein X and Y are independently amino acids.

50. The method according to any one of claims 39-46, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



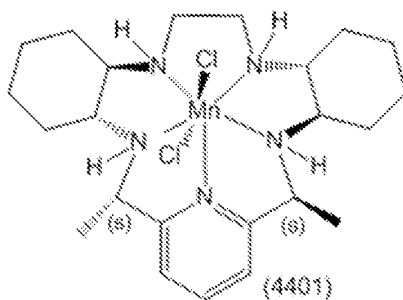
5

51. The method according to any one of claims 39-46, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



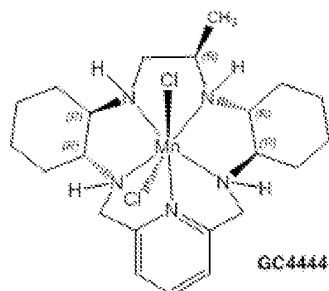
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52. The method according to any one of claims 39-46, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:

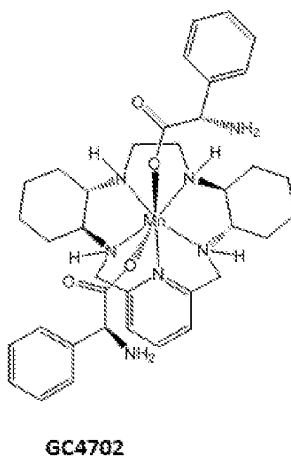


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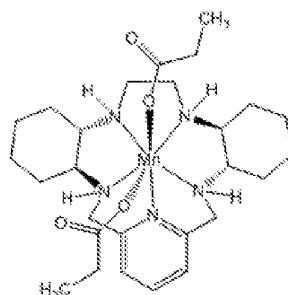
53. The method according to any one of claims 39-46, wherein the pentaaza macrocyclic ring complex is represented by the formula:



54. The method according to any one of claims 39-46, wherein the pentaaza macrocyclic ring complex is represented by the formula:



55. The method according to any one of claims 39-46, wherein the pentaaza macrocyclic ring complex is represented by the formula:

**GC4711**

56. The method according to any of claims 39-55, wherein initial
administration of the pentaaza macrocyclic ring complex in a course of therapy is a
predetermined period of time after initial administration of the adoptive T-cell transfer
therapy.

57. The method according to any of claims 39-56, comprising administering
the adoptive T-cell transfer therapy and pentaaza macrocyclic ring complex to a subject
that is not receiving radiation therapy.

58. The method according to any of claims 39-57, wherein the adoptive T-cell
transfer therapy comprises administering to the subject cancer-specific autologous or
allogeneic T-cells.

59. The method according to any of claims 39-58, wherein the adoptive T-cell
transfer therapy comprises providing autologous tumor infiltrating lymphocytes, antigen-
expanded CD8+ and/or CD4+ T cells, and genetically modified T cells that express T-
cell receptors (TCR) that recognize tumor antigens.

60. The method according to any of claims 39-59, further comprising
administering one or more of an immune checkpoint inhibitor and a cancer vaccine to
the subject, either prior to, concomitantly with, or after administration of one or more of
the adoptive T-cell transfer therapy and pentaaza macrocyclic ring complex.

61. The method according to any of claims 39-60, wherein the cancer is selected from the group consisting of breast cancer, non-small-cell lung cancer, melanoma, renal cell carcinoma, urothelial carcinoma, bladder cancer, pancreatic cancer, head and neck cancers, colorectal cancer, prostate cancer, brain cancer, spindle cell carcinoma, and oral squamous cell carcinoma.

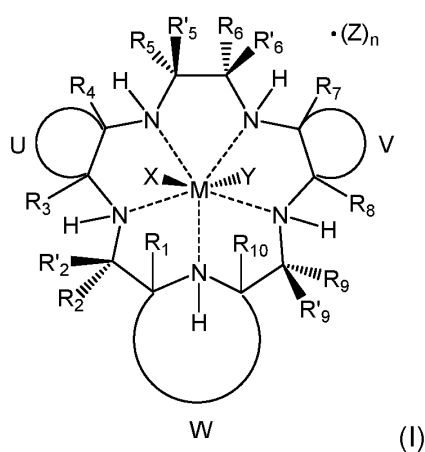
62. The method according to any of claims 39-61, wherein the pentaaza macrocyclic ring complex is administered via at least one of parenteral route and oral route.

10

63. The method according to claim 62, wherein the pentaaza macrocyclic ring complex is administered intraperitoneally or intravenously.

64. A method of treating a cancer in a mammalian subject afflicted with the cancer, the method comprising:
administering to the subject a cancer vaccine;
administering to the subject a pentaaza macrocyclic ring complex corresponding to the formula (I) below, prior to, concomitantly with, or after administration of the cancer vaccine, to increase the response of the cancer to the cancer vaccine,

20



wherein

M is Mn^{2+} or Mn^{3+} ;

R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R₆, R'₆, R₇, R₈, R₉, R'₉, and R₁₀ are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting of -OR₁₁, -NR₁₁R₁₂, -COR₁₁, -CO₂R₁₁, -CONR₁₁R₁₂, -SR₁₁, -SOR₁₁, -SO₂R₁₁, -SO₂NR₁₁R₁₂, -N(OR₁₁)(R₁₂), -P(O)(OR₁₁)(OR₁₂), -P(O)(OR₁₁)(R₁₂), and -OP(O)(OR₁₁)(OR₁₂), wherein R₁₁ and R₁₂ are independently hydrogen or alkyl;

U, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;

V, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;

W, together with the nitrogen of the macrocycle and the carbon atoms of the macrocycle to which it is attached, forms an aromatic or alicyclic, substituted or unsubstituted, saturated, partially saturated or unsaturated nitrogen-containing fused heterocycle having 2 to 20 ring carbon atoms, provided that when W is a fused aromatic heterocycle the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and R₁ and R₁₀ attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent;

X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof;

Z is a counterion;

n is an integer from 0 to 3; and

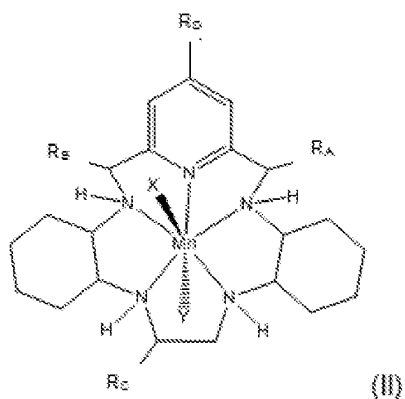
the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.

65. The method according to claim 64, wherein R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R₆, R'₆, R₇, R₈, R₉, R'₉, and R₁₀ are each hydrogen.

66. The method according to claim 64 or 65, wherein W is an unsubstituted pyridine moiety.

67. The method according to any of claims 64-66, wherein U and V are transcyclohexanyl fused rings.

- 5 68. The method according to any of claims 64-67, wherein the pentaaza macrocyclic ring complex is represented by formula (II):



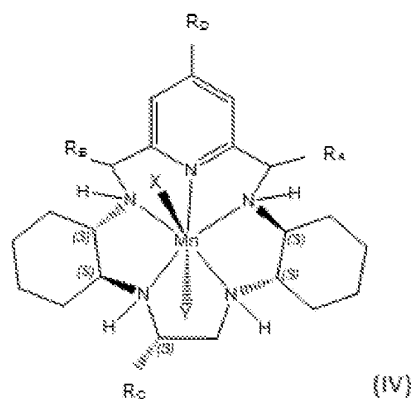
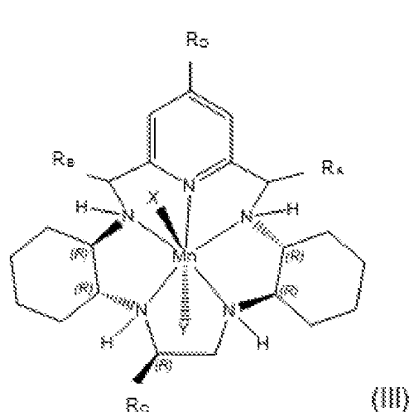
wherein

X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and

R_A, R_B, R_C, and R_D are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting

of -OR₁₁, -NR₁₁R₁₂, -COR₁₁, -CO₂R₁₁, -CONR₁₁R₁₂, -SR₁₁, -SOR₁₁, -SO₂R₁₁, -SO₂NR₁₁R₁₂, -N(OR₁₁)(R₁₂), -P(O)(OR₁₁)(OR₁₂), -P(O)(OR₁₁)(R₁₂), and -OP(O)(OR₁₁)(OR₁₂), wherein R₁₁ and R₁₂ are independently hydrogen or alkyl.

69. The method according to any of claims 64-68, wherein the pentaaza macrocyclic ring complex is represented by formula (III) or formula (IV):



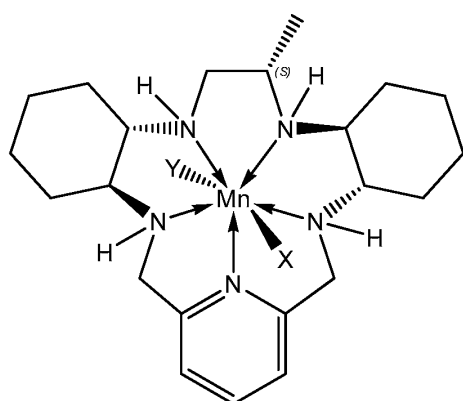
wherein

X and Y represent suitable ligands which are derived from any monodentate or
 5 polydentate coordinating ligand or ligand system or the corresponding anion
 thereof; and

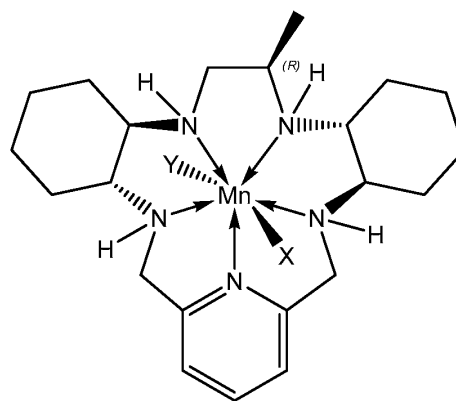
R_A , R_B , R_C , and R_D are independently hydrogen, hydrocarbyl, substituted
 hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected
 from the group consisting

10 of $-OR_{11}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{11}$, $-CONR_{11}R_{12}$, $-SR_{11}$, $-SOR_{11}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$, $-N(OR_{11})(R_{12})$, $-P(O)(OR_{11})(OR_{12})$, $-P(O)(OR_{11})(R_{12})$,
 and $-OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or
 alkyl.

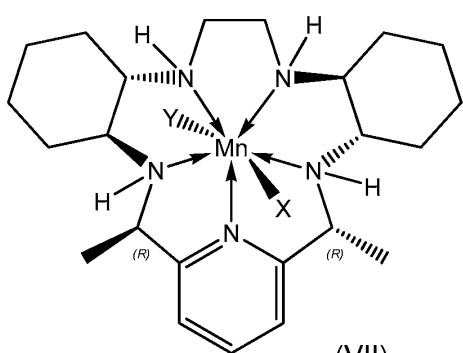
15 70. The method according to any of claims 64-69, wherein the pentaaza
 macrocyclic ring complex is a compound represented by a formula selected from the
 group consisting of formulae (V)-(XVI):



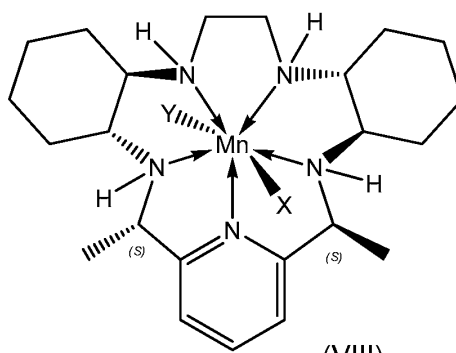
(V)



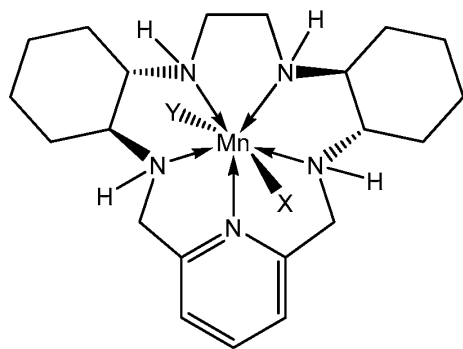
(VI)



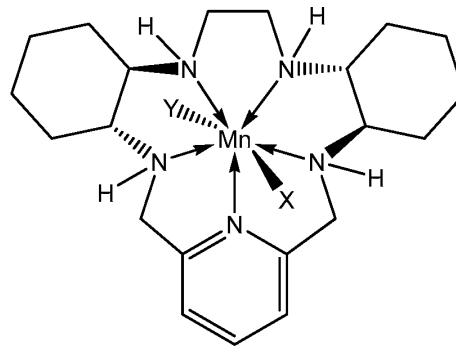
(VII)



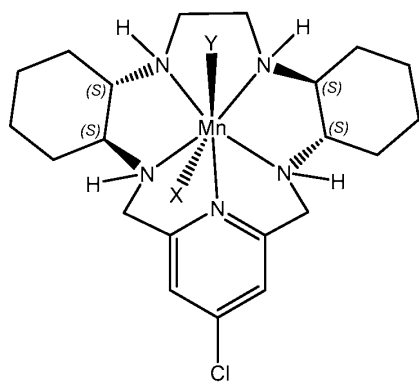
(VIII)



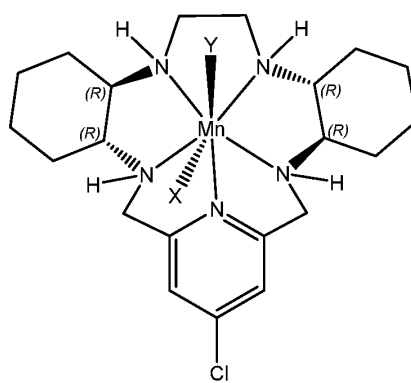
(IX)



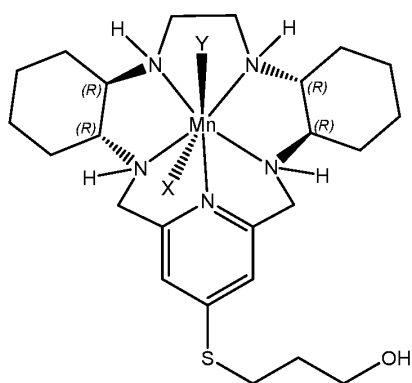
(X)



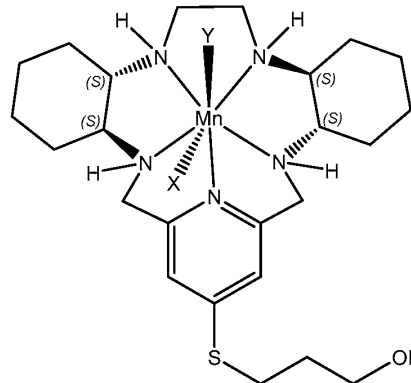
(XI)



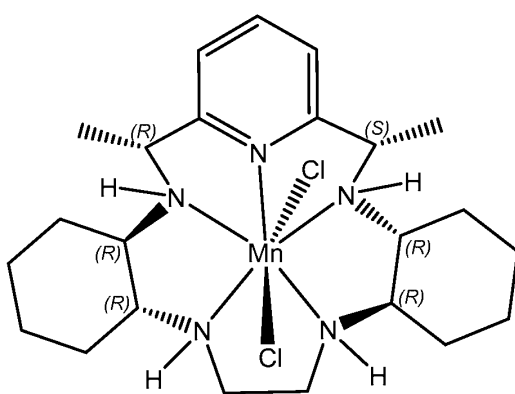
(XII)



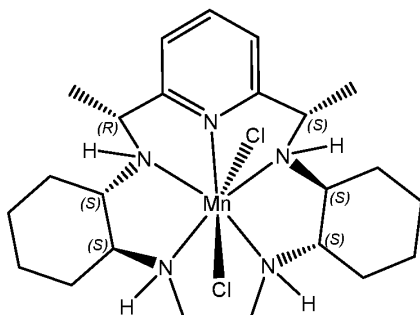
(XIII)



(XIV)



(XV)



(XVI)

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71. The method according to any of claims 64-70, wherein X and Y are independently selected from substituted or unsubstituted moieties of the group consisting of halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen, peroxy, hydroperoxy, alkylperoxy, arylperoxy, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid, aryl carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate, aryl thiocarbamate, alkylaryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate,

tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins, or the corresponding anions thereof;

- or X and Y correspond to $-O-C(O)-X_1$, where each X_1 is $-C(X_2)(X_3)(X_4)$, and
- 5 each X_1 is independently substituted or unsubstituted phenyl or $-C(-X_2)(-X_3)(-X_4)$;
- each X_2 is independently substituted or unsubstituted phenyl, methyl, ethyl or propyl;
- each X_3 is independently hydrogen, hydroxyl, methyl, ethyl, propyl, amino,
- 10 $-X_5C(=O)R_{13}$ where X_5 is NH or O, and R_{13} is C1-C18 alkyl, substituted or unsubstituted aryl or C1-C18 aralkyl, or $-OR_{14}$, where R_{14} is C1-C18 alkyl, substituted or unsubstituted aryl or C1-C18 aralkyl, or together with X_4 is $(=O)$; and
- each X_4 is independently hydrogen or together with X_3 is $(=O)$;
- 15 or X and Y are independently selected from the group consisting of charge-neutralizing anions which are derived from any monodentate or polydentate coordinating ligand and a ligand system and the corresponding anion thereof;
- or X and Y are independently attached to one or more of $R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9$, and R_{10} .

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72. The method according to any of claims 64-71, wherein X and Y are independently selected from the group consisting of fluoro, chloro, bromo, and iodo anions.

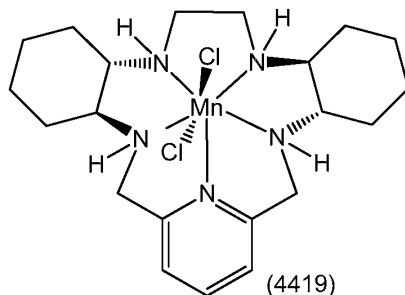
25

73. The method according to any one of claims 64-71, wherein X and Y are independently selected from the group consisting of alkyl carboxylates, aryl carboxylates and arylalkyl carboxylates.

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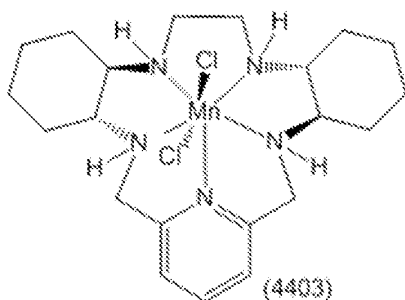
74. The method according to any one of claims 64-71, wherein X and Y are independently amino acids.

75. The method according to any one of claims 64-71, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



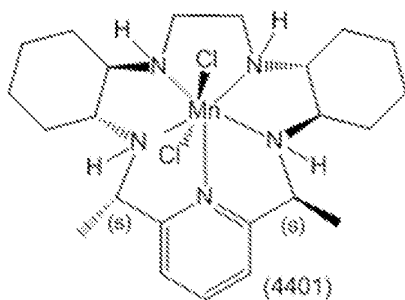
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76. The method according to any one of claims 64-71, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



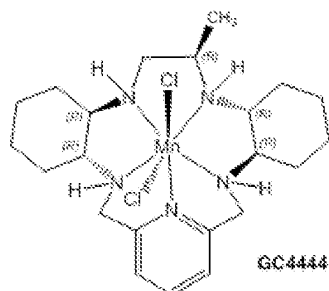
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77. The method according to any one of claims 64-71, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:

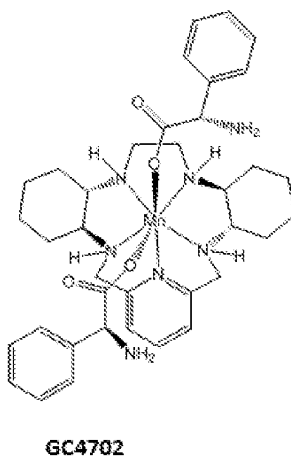


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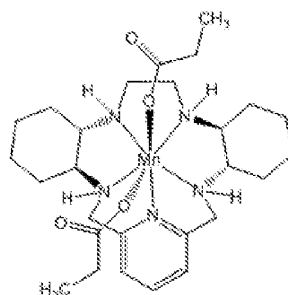
78. The method according to any one of claims 64-71, wherein the pentaaza macrocyclic ring complex is represented by the formula:



5 79. The method according to any one of claims 64-71, wherein the pentaaza macrocyclic ring complex is represented by the formula:



10 80. The method according to any one of claims 64-71, wherein the pentaaza macrocyclic ring complex is represented by the formula:

**GC4711**

81. The method according to any of claims 64-80, wherein initial
administration of the pentaaza macrocyclic ring complex in a course of therapy is a
predetermined period of time after initial administration of the cancer vaccine.

82. The method according to any of claims 64-81, comprising administering
the cancer vaccine and pentaaza macrocyclic ring complex to a subject that is not
receiving radiation therapy.

10

83. The method according to any of claims 64-82, wherein the cancer vaccine
is selected from the group consisting of tumor cell vaccines, antigen vaccines, dendritic
cell vaccines, DNA vaccines and vector based vaccines.

84. The method according to any of claims 64-83, wherein the cancer vaccine
is selected from the group consisting of M-Vax (Avax Technologies), Provenge
(Dendreon), GRNVAC1 (Geron), Bexidex (IDM Pharma), Uvidex (IDM Pharma),
Collidex (IDM Pharma), INGN 225 (Introgen Therapeutics), M3Tk (MolMed), DC-Vax
(Northwest Biotherapeutics), CVax (Prima Biomed), GVAX (Cell Genesys), Lucanix
(NovaRx), Onyvax-P (Onyvax), HSPP-96 Oncophage (Antigenics), BiovaxID (Biovest
International), NeuVax (Apthera), CDX-110 (CeppDex), GV1001 (Pharmexa), CYT004-
MelQbG10 (Cytos Biotechnology), li-Key/HER2/neu (Generex Biotechnology), MAGE-
A3 (Glaxo-SmithKline Biologicals), IDM-2101 (IDM Pharma), IMA901/IMA910 (Immatics
Biotechnologies), melanoma cancer vaccine (Norwood Immunology), inCVAX
(Immunophotonics) and Stimuvax (Oncothyreon).

25

85. The method according to any of claims 64-84, further comprising administering one or more of an immune checkpoint inhibitor and an adoptive T-cell transfer therapy to the subject, either prior to, concomitantly with, or after administration
5 of one or more of the cancer vaccine and pentaaza macrocyclic ring complex.

86. The method according to any of claims 64-85, wherein the cancer is selected from the group consisting of breast cancer, non-small-cell lung cancer, melanoma, renal cell carcinoma, urothelial carcinoma, bladder cancer, pancreatic
10 cancer, head and neck cancers, colorectal cancer, prostate cancer, brain cancer, spindle cell carcinoma, and oral squamous cell carcinoma.

87. The method according to any of claims 64-86, wherein the pentaaza macrocyclic ring complex is administered via at least one of parenteral route and oral
15 route.

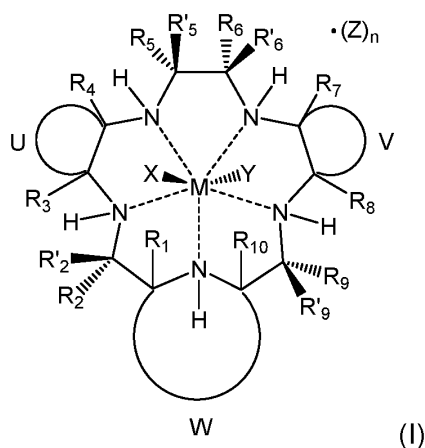
88. The method according to claim 87, wherein the pentaaza macrocyclic ring complex is administered intraperitoneally or intravenously.

20 89. A method of treating a viral infection in a mammalian subject in need thereof, comprising.

administering to the subject at least one of an immune checkpoint inhibitor, an adoptive T-cell transfer therapy, and a vaccine; and

administering to the subject a pentaaza macrocyclic ring complex
25 corresponding to the formula (I) below, prior to, concomitantly with, or after the at least one immune checkpoint inhibitor, adoptive T-cell transfer therapy, and vaccine, to increase the effectiveness of the at least one immune checkpoint, adoptive T-cell transfer therapy, and vaccine in treating the viral infection,

30



wherein

M is Mn^{2+} or Mn^{3+} ;

R_1 , R_2 , R'_2 , R_3 , R_4 , R_5 , R'_5 , R_6 , R'_6 , R_7 , R_8 , R_9 , R'_9 , and R_{10} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting of $-OR_{11}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{11}$, $-CONR_{11}R_{12}$, $-SR_{11}$, $-SOR_{11}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$, $-N(OR_{11})(R_{12})$, $-P(O)(OR_{11})(OR_{12})$, $-P(O)(OR_{11})(R_{12})$, and $-OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or alkyl;

U, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;

V, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;

W, together with the nitrogen of the macrocycle and the carbon atoms of the macrocycle to which it is attached, forms an aromatic or alicyclic, substituted or unsubstituted, saturated, partially saturated or unsaturated nitrogen-containing fused heterocycle having 2 to 20 ring carbon atoms, provided that when W is a fused aromatic heterocycle the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and R_1 and R_{10} attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent;

X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof;

Z is a counterion;

n is an integer from 0 to 3; and

the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.

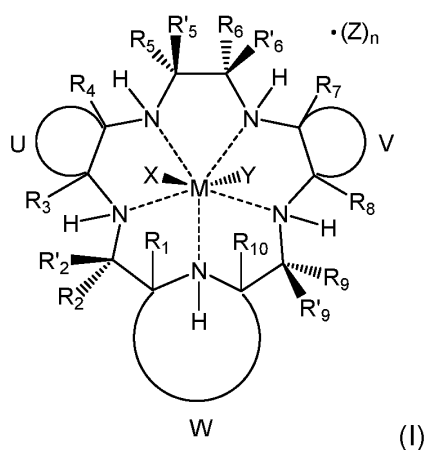
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90. A kit comprising:

at least one of an immune checkpoint inhibitor, T-cells for an adoptive T-cell transfer therapy, and a cancer vaccine; and

a pentaaza macrocyclic ring complex according to formula (I),

10



wherein

M is Mn^{2+} or Mn^{3+} ;

15 $R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9,$ and R_{10} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting of $-OR_{11}, -NR_{11}R_{12}, -COR_{11}, -CO_2R_{11}, -CONR_{11}R_{12}, -SR_{11}, -SOR_{11}, -SO_2R_{11}, -SO_2NR_{11}R_{12}, -N(OR_{11})(R_{12}), -P(O)(OR_{11})(OR_{12}), -P(O)(OR_{11})(R_{12}),$ and $-OP(O)(OR_{11})(OR_{12}),$

20 wherein R_{11} and R_{12} are independently hydrogen or alkyl;

U, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;

V, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;

5 W, together with the nitrogen of the macrocycle and the carbon atoms of the macrocycle to which it is attached, forms an aromatic or alicyclic, substituted or unsubstituted, saturated, partially saturated or unsaturated nitrogen-containing fused heterocycle having 2 to 20 ring carbon atoms, provided that when W is a fused aromatic heterocycle the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and R₁ and R₁₀ attached to the carbon atoms which are both part of
10 the heterocycle and the macrocycle are absent;

X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof;

Z is a counterion;

n is an integer from 0 to 3; and

15 the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.