

CARCINOGENESIS REDUCTION WITH PENTAAZA MACROCYCLIC RING COMPLEX

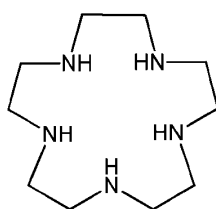
Cross Reference to Related Applications

[0001] The present application claims benefit of U.S. Provisional Patent Application Serial No. 63/528,194, filed on July 21, 2023, which application is incorporated by reference herein in its entirety.

5 [0002] This invention was made with government support under grant number 80NSSC18K1676, awarded by the National Aeronautics and Space Administration (NASA). The government has certain rights in the invention.

[0003] The present disclosure generally relates to therapies for treating and/or reducing the risk of carcinogenesis in a mammalian subject, by administration of a
10 pentaaza macrocyclic ring complex. It further relates to therapies for treating and/or reducing the risk of carcinogenesis resulting radiation therapy that is provided to the mammalian subject as a course of treatment for cancer, as well as carcinogenesis resulting from exposure to other sources of radiation, such as radiation exposure occurring during space travel. It further relates to therapies for increasing the life span,
15 actual or expected, of a mammalian subject.

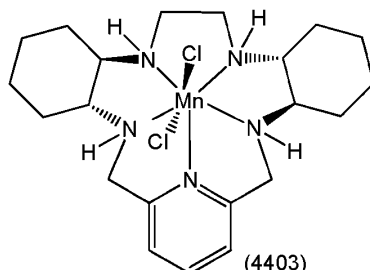
[0004] Transition metal-containing pentaaza macrocyclic ring complexes having the macrocyclic ring system corresponding to Formula A have been shown to be effective in a number of animal and cell models of human disease, as well as in treatment of conditions afflicting human patients.



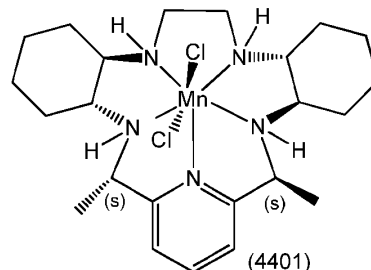
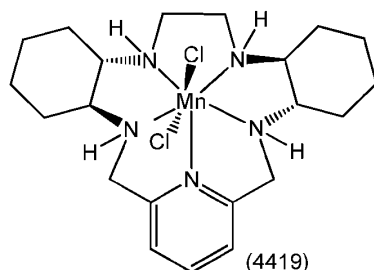
20 FORMULA A

For example, in a rodent model of colitis, one such compound, GC4403, has been reported to very significantly reduce the injury to the colon of rats subjected to an

experimental model of colitis (see Cuzzocrea *et al.*, *Europ. J. Pharmacol.*, 432, 79-89 (2001)).



- GC4403 has also been reported to attenuate the radiation damage arising both in a
- 5 clinically relevant hamster model of acute, radiation-induced oral mucositis (Murphy *et al.*, *Clin. Can. Res.*, 14(13), 4292 (2008)), and lethal total body irradiation of adult mice (Thompson *et al.*, *Free Radical Res.*, 44(5), 529-40 (2010)). Similarly, another such compound, GC4419, has been shown to attenuate VEGFr inhibitor-induced pulmonary disease in a rat model (Tuder, *et al.*, *Am. J. Respir. Cell Mol. Biol.*, 29, 88-97 (2003)).
- 10 Additionally, another such compound, GC4401 has been shown to provide protective effects in animal models of septic shock (S. Cuzzocrea, *et al.*, *Crit. Care Med.*, 32(1), 157 (2004) and pancreatitis (S. Cuzzocrea, *et al.*, *Shock*, 22(3), 254-61 (2004)).



- [0005] Certain of these compounds have also been shown to possess potent
- 15 anti-inflammatory activity and prevent oxidative damage *in vivo*. For example, GC4403 has been reported to inhibit inflammation in a rat model of inflammation (Salvemini, *et al.*, *Science*, 286, 304 (1999)), and prevent joint disease in a rat model of collagen-induced arthritis (Salvemini *et al.*, *Arthritis & Rheumatism*, 44(12), 2009-2021 (2001)). Yet others of these compounds, MdPAM and MnBAM, have shown *in vivo* activity in the
- 20 inhibition of colonic tissue injury and neutrophil accumulation into colonic tissue (Weiss *et al.*, *The Journal of Biological Chemistry*, 271(42), 26149-26156 (1996)). In addition,

these compounds have been reported to possess analgesic activity and to reduce inflammation and edema in the rat-paw carrageenan hyperalgesia model, see, e.g., U.S. Pat. No. 6,180,620.

[0006] Compounds of this class have also been shown to be safe and effective in the prevention and treatment of disease in human subjects. For example, GC4419 has been shown to reduce oral mucositis in head-and-neck cancer patients undergoing chemoradiation therapy (Anderson, C., *Phase IIB, Randomized, Double-Blind Trial of GC4419 Versus Placebo to Reduce Severe Oral Mucositis Due to Concurrent Radiotherapy and Cisplatin for Head and Neck Cancer*, J. Clin. Oncol. 37, 1-10 (2019))) and to reduce kidney damage from cisplatin therapy for cancer (Griffin et al, *Effects of Avasopasem Manganese on Cisplatin-Induced AKI and CKD*, Abstract, Kidney Week (2023)).

[0007] In addition, transition metal-containing pentaaza macrocyclic ring complexes corresponding to this class have shown efficacy in the treatment of various cancers. For example, certain compounds corresponding to this class have been provided in combination with agents such as paclitaxel and gemcitabine to enhance cancer therapies, such as in the treatment of colorectal cancer and lung cancer (non-small cell lung cancer) (see, e.g., U.S. Patent No. 9,198,893) The 4403 compound above has also been used for treatment in *in vivo* models of Meth A spindle cell squamous carcinoma and RENCA renal carcinoma (Samlowski et al., *Nature Medicine*, 9(6), 750-755 (2003), and has also been used for treatment in *in vivo* models of spindle-cell squamous carcinoma metastasis (Samlowski et al., *Madame Curie Bioscience Database (Internet)*, 230-249 (2006)). Transition metal-containing pentaaza macrocyclic ring complexes have also shown beneficial effects when combined with radiation therapy (Sishc et al., *Sci. Transl. Med.*, 13 eabb3768 (2020); Taniguchi et al., *The Lancet Oncology*, 24(12), 1387-1398 (2023)), as well as with chemotherapeutic agents such as cisplatin (Mohanty et al., *GC4419 Enhances the Response of Non-Small Cell Lung Carcinoma Cell Lines to Cisplatin and Cisplatin Plus Radiation Through a ROS-Mediated Pathway*, AACR Annual Meeting, Abstract 2929 (2018)), and tamoxifen (Zhu et al., *Nature Communications*, 10(2399), 1-15 (2019)).

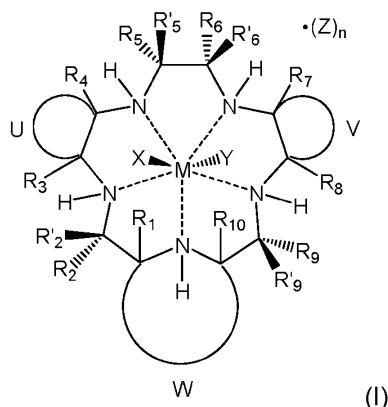
[0008] Carcinogenesis, or the initiation of cancer formation in a subject, can be caused by exposure of the subject to radiation, by other agents, or spontaneously.

Radiation may cause carcinogenesis in the course of receiving radiation therapy for to treat cancer, via exposure to other radiation sources or through combined exposure to multiple sources. A subject receiving radiation therapy for the treatment of cancer may thus put themselves at higher risk for the development of a subsequent cancer (i.e. a radiogenic cancer) at some future point in time (Zhang *et al.*, *Radiation Oncology*, 10 (107) (2015)). Some of the cancers associated with radiation exposure include leukemia, breast, bladder, colon, liver, lung, esophagus, ovarian, multiple myeloma, spleen, and stomach cancers. Further, pediatric patients often have higher radiosensitivity than adults due to their rapidly dividing tissues (Sulieman *et al.*, *Radiation Physics and Chemistry*, Vol. 200, 110328 (2022); Newhauser *et al.*, *Frontiers in Oncology*, 6 (2016)). Other sources of radiation exposure can include environmental exposure, such as excessive sun exposure (a major contributing factor to melanomas) (Sample *et al.*, *Photodermatol Photoimmunol Photomed*, 34(1): 13-24 (2018)) as well as accidental or occupational exposure in a lab, hospital, or other environment. There is also increasing interest in understanding and mitigating the ill effects from the radiation exposure that can accompany space travel (Roig *et al.*, *Int J Radiat Biol*, 86(3), 194-204 (2010); Ding *et al.*, *Mutagenesis*, 30(5) 685-694 (2015)).

[0009] Accordingly, a need remains for therapies to reduce the risk of carcinogenesis and radiation-induced cancers for subjects having been exposed to radiation. There also remains a need for therapies to treat persons having received a therapeutic or non-therapeutic dose of radiation, to reduce the likelihood of secondary (radiogenic) cancer development caused by the dose of radiation.

[0010] Briefly, therefore, aspects of the present disclosure are directed to a method of reducing the risk of carcinogenesis in a mammalian subject, the method comprising:

administering to the mammalian subject a therapeutically effective amount of a pentaaza macrocyclic ring complex corresponding to the Formula (I) below:



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 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.

[0011] Aspects of the present disclosure are further directed to a method of extending lifespan in a mammalian subject, the method comprising administering to the mammalian subject a therapeutically effective amount of a pentaaza macrocyclic ring complex corresponding to the Formula (I).

Brief Description of the Drawings

[0012] Figs. 1A-1D are plots showing the long-term survival of irradiated female BALB/c mice of approximately 84 days of age subjected to a single γ -ray exposure of 0.75 or 1.5 Gy, and treated or not with GC4419.

5 [0013] Figs. 2A-2D are plots showing the long term survival of irradiated female BALB/c mice of approximately 84 days of age subjected to a single simulated galactic cosmic radiation, or GCRsim exposure of 0.4 or 0.75 Gy, and treated or not with GC4419.

10 [0014] Fig. 3A is an expansion of the plot in Fig. 3B showing only the range of % Survival from 95% to 100% over the time period through approximately 400 days post irradiation. 3B is a plot showing long-term survival through the entire study of unirradiated "control" female BALB/c mice of approximately 84 days of age at the beginning of the study, treated or not with GC4419. Fig. 3C is an expansion of the plot in Fig. 3A showing only the range of % Survival from 70% to 100%.

15 [0015] Fig. 4A is a bar chart showing the % of female BALB/c mice of approximately 84 days of age subjected to a single γ -ray (0.75 or 1.5 Gy) or simulated galactic cosmic radiation (0.4 or 0.75 Gy) exposure, or not exposed to radiation

("control"), and treated or not with GC4419 who had lung masses at necropsy. Fig. 4B is a bar chart showing the % who had ovarian masses or hemorrhagic cysts at necropsy.

[0016] Abbreviations and Definitions

5 [0017] The following definitions and methods are provided to better define the present invention and to guide those of ordinary skill in the art in the practice of the present invention. Unless otherwise noted, terms are to be understood according to conventional usage by those of ordinary skill in the relevant art.

[0018] "Acyl" means a -COR moiety where R is alkyl, haloalkyl, optionally substituted aryl, or optionally substituted heteroaryl as defined herein, e.g., acetyl, trifluoroacetyl, benzoyl, and the like.

[0019] "Acyloxy" means a -OCOR moiety where R is alkyl, haloalkyl, optionally substituted aryl, or optionally substituted heteroaryl as defined herein, e.g., acetyl, trifluoroacetyl, benzoyl, and the like.

15 [0020] "Alkoxy" means a -OR moiety where R is alkyl as defined above, e.g., methoxy, ethoxy, propoxy, or 2-propoxy, n-, iso-, or tert-butoxy, and the like.

[0021] "Alkyl" means a linear saturated monovalent hydrocarbon moiety such as of one to six carbon atoms, or a branched saturated monovalent hydrocarbon moiety, such as of three to six carbon atoms, e.g., C₁-C₆ alkyl groups such as methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), pentyl (including all isomeric forms), and the like.

[0022] Moreover, unless otherwise indicated, the term "alkyl" as used herein is intended to include both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Indeed, unless otherwise indicated, all groups recited herein are intended to include both substituted and unsubstituted options.

[0023] The term "C_{x-y}" when used in conjunction with a chemical moiety, such as alkyl and aralkyl, is meant to include groups that contain from x to y carbons in the chain. For example, the term C_{x-y} alkyl refers to substituted or unsubstituted saturated hydrocarbon groups, including straight chain alkyl and branched chain alkyl groups that contain from x to y carbon atoms in the chain.

[0024] "Alkylene" means a linear saturated divalent hydrocarbon moiety, such as of one to six carbon atoms, or a branched saturated divalent hydrocarbon moiety, such as of three to six carbon atoms, unless otherwise stated, e.g., methylene, ethylene, propylene, 1-methylpropylene, 2-methylpropylene, butylene, pentylene, and
5 the like.

[0025] The term "carcinogenesis" as used herein refers to the initiation of cancer formation by transformation of normal cells into cancer cells, such as by exposure to a therapeutic or environmental trigger, including radiation exposure incurred as a part of a cancer therapy, or occurring spontaneously.

10 [0026] The term "radiogenic cancer" as used herein means a cancer caused at least in part by an exposure to ionizing radiation, including radiation exposure incurred as a part of a cancer therapy. Examples of radiogenic cancers caused by radiation exposure may typically include leukemia, breast, bladder, colon, liver, spleen lung, esophagus, ovarian, multiple myeloma, and stomach cancers, as well as prostate,
15 oral cavity, nasal cavity/sinus, pharyngeal and laryngeal, and pancreatic cancers.

[0027] The term "lifespan" as used herein refers to a lifespan metric for a subject, such as actual observed lifespan (the number of years the subject actually lives), or an expected lifespan (the number of years the subject is expected to live).

[0028] "Alkenyl" a linear unsaturated monovalent hydrocarbon moiety, such
20 as of two to six carbon atoms, or a branched saturated monovalent hydrocarbon moiety, such as of three to six carbon atoms, e.g., ethenyl (vinyl), propenyl, 2-propenyl, butenyl (including all isomeric forms), pentenyl (including all isomeric forms), and the like.

[0029] "Alkaryl" means a monovalent moiety derived from an aryl moiety by replacing one or more hydrogen atoms with an alkyl group.

25 [0030] "Alkenylcycloalkenyl" means a monovalent moiety derived from an alkenyl moiety by replacing one or more hydrogen atoms with a cycloalkenyl group.

[0031] "Alkenylcycloalkyl" means a monovalent moiety derived from a cycloalkyl moiety by replacing one or more hydrogen atoms with an alkenyl group.

[0032] "Alkylcycloalkenyl" means a monovalent moiety derived from a
30 cycloalkenyl moiety by replacing one or more hydrogen atoms with an alkyl group.

[0033] "Alkylcycloalkyl" means a monovalent moiety derived from a cycloalkyl moiety by replacing one or more hydrogen atoms with an alkyl group.

[0034] "Alkynyl" means a linear unsaturated monovalent hydrocarbon moiety, such of two to six carbon atoms, or a branched saturated monovalent hydrocarbon moiety, such as of three to six carbon atoms, e.g., ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like.

[0035] "Alkoxy" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with a hydroxy group.

[0036] "Amino" means a $-NR^aR^b$ group where R^a and R^b are independently hydrogen, alkyl or aryl.

[0037] "Aralkyl" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with an aryl group.

[0038] "Aryl" means a monovalent monocyclic or bicyclic aromatic hydrocarbon moiety of 6 to 10 ring atoms e.g., phenyl or naphthyl.

[0039] "Cycle" means a carbocyclic saturated monovalent hydrocarbon moiety of three to ten carbon atoms.

[0040] "Cycloalkyl" means a cyclic saturated monovalent hydrocarbon moiety of three to ten carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, and the like.

[0041] "Cycloalkylalkyl" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with a cycloalkyl group, e.g., cyclopropylmethyl, cyclobutylmethyl, cyclopentylethyl, or cyclohexylethyl, and the like.

[0042] "Cycloalkylcycloalkyl" means a monovalent moiety derived from a cycloalkyl moiety by replacing one or more hydrogen atoms with a cycloalkyl group.

[0043] "Cycloalkenyl" means a cyclic monounsaturated monovalent hydrocarbon moiety of three to ten carbon atoms, e.g., cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl, and the like.

[0044] "Cycloalkenylalkyl" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with a cycloalkenyl group, e.g.,

cyclopropenylmethyl, cyclobutenylmethyl, cyclopentenylethyl, or cyclohexenylethyl, and the like.

[0045] "Ether" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with an alkoxy group.

5 [0046] "Halo" means fluoro, chloro, bromo, or iodo, preferably fluoro or chloro.

[0047] "Heterocycle" or "heterocyclyl" means a saturated or unsaturated monovalent monocyclic group of 4 to 8 ring atoms in which one or two ring atoms are heteroatom selected from N, O, or S(O)_n, where n is an integer from 0 to 2, the remaining ring atoms being C. The heterocyclyl ring is optionally fused to a (one) aryl or
10 heteroaryl ring as defined herein provided the aryl and heteroaryl rings are monocyclic. The heterocyclyl ring fused to monocyclic aryl or heteroaryl ring is also referred to in this Application as "bicyclic heterocyclyl" ring. Additionally, one or two ring carbon atoms in the heterocyclyl ring can optionally be replaced by a –CO– group. More specifically the term heterocyclyl includes, but is not limited to, pyrrolidino, piperidino, homopiperidino,
15 2-oxopyrrolidinyl, 2-oxopiperidinyl, morpholino, piperazino, tetrahydropyranyl, thiomorpholino, and the like. When the heterocyclyl ring is unsaturated it can contain one or two ring double bonds provided that the ring is not aromatic. When the heterocyclyl group is a saturated ring and is not fused to aryl or heteroaryl ring as stated above, it is also referred to herein as saturated monocyclic heterocyclyl.

20 [0048] "Heteroaryl" means a monovalent monocyclic or bicyclic aromatic moiety of 5 to 10 ring atoms where one or more, preferably one, two, or three, ring atoms are heteroatom selected from N, O, or S, the remaining ring atoms being carbon. Representative examples include, but are not limited to, pyrrolyl, pyrazolyl, thienyl, thiazolyl, imidazolyl, furanyl, indolyl, isoindolyl, oxazolyl, isoxazolyl, benzothiazolyl,
25 benzoxazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl, and the like.

[0049] "Nitro" means –NO₂.

[0050] "Organosulfur" means a monovalent moiety a –SR group where R is hydrogen, alkyl or aryl.

30 [0051] "Substituted alkyl," "substituted cycle," "substituted phenyl," "substituted aryl," "substituted heterocycle," and "substituted nitrogen heterocycles"

means an alkyl, cycle, aryl, phenyl, heterocycle or nitrogen-containing heterocycle, respectively, optionally substituted with one, two, or three substituents, such as those independently selected from alkyl, alkoxy, alkoxyalkyl, halo, hydroxy, hydroxyalkyl, or organosulfur. Generally, the term "substituted" includes groups that are substituted with
5 any one or more of C₁₋₄alkyl, C₂₋₄alkenyl, halogen, alcohol and/or amine.

[0052] "Thioether" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with an -SR group wherein R is alkyl.

[0053] As used herein, (i) the compound referred to herein and in the Figures as compound 401, 4401 or GC4401 is a reference to the same compound, (ii) the
10 compound referred to herein and in the Figures as compound 403, 4403 or GC4403 is a reference to the same compound, (iii) the compound referred to herein and in the Figures as compound 419, 4419 or GC4419 is a reference to the same compound, and (iv) the compound referred to herein and in the Figures as compound 444, 4444 or GC4444 is a reference to the same compound.

[0054] Furthermore, the use of the term "consisting essentially of," in referring to a method of treatment, means that the method substantially does not involve providing another therapy and/or another active agent in amounts and/or under conditions that would be sufficient to provide the treatment, and which are other than the therapies and/or active agents specifically recited in the claim. Similarly, the use of
20 the term "consisting essentially of," in referring to a kit for treatment, means that the kit substantially does not include another therapy and/or another active agent provided in amounts and/or under conditions that would be sufficient to provide the treatment, and which are other than the therapies and/or active agents specifically recited in the claim.

Detailed Description

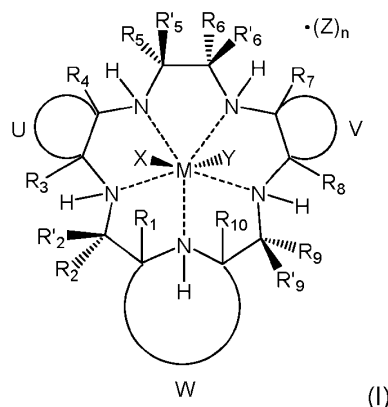
[0055] In one embodiment, aspects of the present disclosure are directed to a
25 method of reducing the risk of carcinogenesis in a mammalian subject, by administering a pentaaza macrocyclic ring complex that is capable of reducing the likelihood of a cancer developing in the subject. According to certain aspects, the pentaaza macrocyclic ring complex may be provided to a subject that is a member of a patient
30 population that is at increased risk of carcinogenesis compared to the general population, such as a subject that has been exposed to radiation. According to certain aspects, the pentaaza macrocyclic ring complex may be provided to a subject that has

received a non-therapeutic dose of radiation, such as via accidental exposure in an occupational or hazardous environmental setting, or during space travel. The pentaaza macrocyclic ring complex is capable of reducing onset of cancer formation to reduce the likelihood that such subjects will experience negative effects from such radiation

- 5 exposure. According to yet another example, the administration of the pentaaza macrocyclic ring complex maybe provided to reduce the risk of carcinogenesis in a mammalian subject, so as to increase the lifespan of the subject.

[0056] According to certain embodiments, a method of reducing the risk of carcinogenesis in the mammalian subject comprises administering to the mammalian
10 subject a therapeutically effective amount of a pentaaza macrocyclic ring complex corresponding to the Formula (I) below:

[0057]



[0058]

[0059] wherein

[0060] M is Mn^{2+} or Mn^{3+} ;

[0061] 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;

[0062] 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;

[0063] 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;

[0064] 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;

[0065] X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof;

[0066] Z is a counterion;

[0067] n is an integer from 0 to 3; and

[0068] the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.

[0069] According to one embodiment, the pentaaza macrocyclic ring complex is administered to a mammalian subject that is a part of a patient population having an increased risk of carcinogenesis as compared to the general population. For example, according to certain aspects, the mammalian subject may be at increased risk of developing cancers due to prior exposure radiation. According to certain aspects, the subject may be at increased risk of carcinogenesis due to prior exposure to therapeutic radiation, such as exposure to radiation provided as a course of therapy for cancer treatment. According to yet another aspect the subject may be one who will be at increased risk of developing cancers because of a planned therapeutic radiation exposure, such as a subject who has been diagnosed with cancer and will be receiving radiation therapy for treatment. In one embodiment, the subject may be a pediatric

patient who either has received, is currently receiving, or is planning to receive, radiation therapy, as pediatric patients can be particularly susceptible to radiogenic cancer formation following radiation therapy. Pediatric patients may be those 21 and younger, 18 and younger, or even 16 and younger, and including children and infants. According to another aspect, the subject may be one who has a high risk of non-therapeutic exposure, such as due to work in a high-risk occupation, or engagement in other activities, where accidental radiation exposure is likely.

[0070] According to certain other aspects, the subject may be at increased risk due to exposure to non-therapeutic radiation, such as accidental or unintentional exposure that occurs as a result of an occupational or environmental hazard. Non-therapeutic radiation exposure may result from a wide variety of commercial and non-commercial activities including, but not limited to activities in industries such as utility and power, oil/gas petrochemical, chemical/plastics, automatic ventilation control (cooking, smoking, etc.), heavy industrial manufacturing, environmental toxicology and remediation, biomedicine, cosmetic/perfume, pharmaceutical, transportation, emergency response and law enforcement, military or terrorist activities, and detection (e.g., hazardous leaks or spills). In one embodiment, for example, the exposure to radiation may result from the excavation and/or clean-up of radioactive material from air, groundwater, surface water, sediment and/or soil. As yet another example of non-therapeutic radiation exposure, subjects traveling to the Earth's upper atmosphere and beyond, including space travel beyond Earth's orbit, can be exposed to the excessive levels of radiation that is present outside the protective shield provided by the Earth's atmosphere. This radiation can include any of galactic cosmic ray (GCR) radiation and γ -ray radiation that can increase the risk of radiogenic cancer formation. Accordingly, in certain embodiments, the subject may be one that previously has, will be, or is currently engaged in travel to the Earth's upper atmosphere or into space.

[0071] In various embodiments, the source of radiation may be any source of radiation used for therapeutic treatment, such as in the treatment and eradication of cancer. The source of radiation can also include non-therapeutic sources of radiation that are not conventionally used for therapeutic treatment. Sources of radiation can include ionizing radiation, such as photon radiation including any one or more of x-rays and gamma rays, and particle radiation including any one or more of electrons, protons, neutrons, carbon ions, alpha particles and beta particles. Cosmic ray

radiation is another source of ionizing radiation. Other sources of radiation typically referred to as non-ionizing radiation can include radio waves, microwaves, and visible or ultraviolet light waves.

[0072] According to yet another embodiment, the pentaaza macrocyclic ring complex is administered to a mammalian subject to increase the lifespan of the subject. The subject may be one who is at increased risk of carcinogenesis, or may be a subject that is not at risk of increased carcinogenesis, such as a subject that has not been exposed to therapeutic radiation or excessive levels of non-therapeutic radiation. For example, the subject may be one that has not had, and does not have, cancer, and has not and will not be subject to therapeutic radiation. By reducing the likelihood of carcinogenesis even in those subjects having otherwise average risk of developing cancer as compared to the general population, the administration of the pentaaza macrocyclic ring complex can increase lifespan and long term survival of such subjects. According to yet another aspect, the increase in lifespan may be due to reduction in the likelihood or extent of another, non-carcinogenic cause, such as a non-cancer disease or disorder, or to reduction in the rate or extent of a non-disease biological process, such as aging. Such aging may include or be reflective of alterations in mitochondrial function, in cell senescence, or in another biological process. The increase in lifespan may either be an increase in actual observed lifespan, or in expected lifespan.

[0073] According to certain embodiments, the pentaaza macrocyclic ring complex is administered to a person afflicted with cancer, and who is either receiving or will receive one or more doses of radiation as a part of a course of radiation therapy to treat the cancer. According to certain aspects, the pentaaza macrocyclic ring complex can be administered before, during or after a dose of radiation provided during a course of therapy provided to treat cancer. For example, according to certain aspects, the pentaaza macrocyclic ring complex can be administered up to 1 min, 5 mins, 15 mins, 30 mins, 1 hour, 6 hours, 12 hours, 1 day, 3 days, 5 days, 1 week, 2 weeks, 1 month, 3 months and/or 6 months before a dose of radiation provided during a course of therapy provided to treat cancer, such as before a first dose or a subsequent dose of radiation provided during a course of radiation therapy. As yet another example, the pentaaza macrocyclic ring complex can be administered at least one hour, at least one day, at least 3 days, at least 5 days, at least a week, at least 2

weeks, at least a month, at least 3 months, at least 6 months, at least a year, or at least 2 years, after a dose of radiation provided during a course of radiation therapy to treat cancer, such as after a last dose of radiation provided during a course of radiation therapy. According to yet another embodiment, the pentaaza macrocyclic ring complex is administered both before and after a dose of radiation provided during a course of radiation therapy to treat cancer.

[0074] According to yet another embodiment, the pentaaza macrocyclic ring complex may be administered any of before, during, and after a course of radiation therapy, such as before a first dose of radiation, at one or more intervals between the first and last doses of radiation, and after a last dose of radiation has been provided during a course of radiation therapy. The pentaaza macrocyclic ring complex can be administered as a single dose or multiple doses during any of these intervals. For example, according to one embodiment, the pentaaza macrocyclic ring complex can be administered as a single dose before the onset of radiation therapy, with multiple subsequent doses being administered during the course of radiation therapy (e.g. between subsequent radiation doses), and/or after the course of radiation therapy has concluded. In one embodiment, the pentaaza macrocyclic ring complex can be administered to a subject who was previously afflicted with cancer, but whose cancer is in remission following prior treatment with radiation therapy. That is, the administration of the pentaaza macrocyclic ring cancer can reduce the risk of carcinogenesis in a subject no longer afflicted with cancer, but at increased risk of a radiogenic cancer (second cancer) due to prior radiation exposure.

[0075] According to certain embodiments, the pentaaza macrocyclic ring complex is administered to a person who has traveled beyond the upper atmosphere of the Earth, or who currently is engaged in such travel or is planning to engage in such travel. For example, according to one embodiment, the pentaaza macrocyclic ring complex is administered before, during or after an exposure to cosmic ray or gamma ray radiation occurring as a part of travel beyond the upper atmosphere of the Earth. As an example, according to certain embodiments, the pentaaza macrocyclic ring complex is administered up to 1 min, 5 mins, 15 mins, 30 mins, 1 hour, 6 hours, 12 hours, 1 day, 3 days, 5 days, 1 week, 2 weeks, 1 month, 3 months and/or 6 months before an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth. As yet another example, according to certain

embodiments, the pentaaza macrocyclic ring complex is administered at least one hour, at least one day, at least 3 days, at least 5 days, at least a week, at least 2 weeks, at least a month, at least 3 months, at least 6 months, at least a year, or at least 2 years, after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth. According to certain aspects, the pentaaza macrocyclic ring complex is administered both before and after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth. According to yet another aspect, multiple doses of the pentaaza macrocyclic ring complex are administered after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

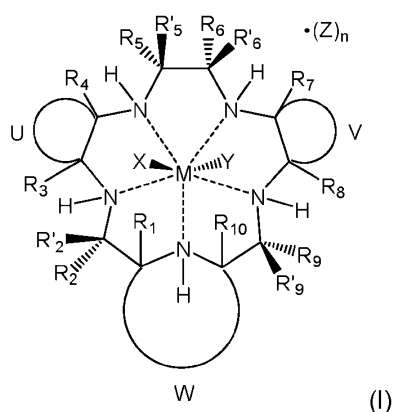
[0076] According to certain aspects, the administration of the pentaaza macrocyclic ring complex to the mammalian subject reduces the likelihood that the subject develops a cancer, which may be a radiogenic or other cancer, such as for example any of leukemia, lymphoma, breast, bladder, colon, liver, lung, esophagus, ovarian, multiple myeloma, spleen, and stomach cancers, as compared to such risk in the absence of administration of the pentaaza macrocyclic ring complex. According to one embodiment, the administration of the pentaaza macrocyclic ring complex to the mammalian subject reduces the risk of lung tumors in the subject. According to another embodiment, the administration of the pentaaza macrocyclic ring complex to the mammalian subject reduces the risk of liver tumors in the subject. According to one embodiment, the administration of the pentaaza macrocyclic ring complex to the mammalian subject reduces the risk of tumors of the spleen in the subject. According to one embodiment, the administration of the pentaaza macrocyclic ring complex to the mammalian subject reduces the risk of ovarian tumors in the subject. According to one embodiment, the administration of the pentaaza macrocyclic ring complex to the mammalian subject reduces the risk of leukemia and/or lymphoma in the subject.

[0077] According to yet another embodiment, a kit for reducing carcinogenesis and/or increasing the lifespan of a mammalian subject is provided, the kit comprising the pentaaza macrocyclic ring complex corresponding to Formula (I), and instructions for administering a therapeutically effective amount of the pentaaza macrocyclic ring complex in accordance with any of the methods disclosed herein.

[0078] Further disclosure of treatment according to aspects herein are provided below.

Transition Metal Pentaaza Macrocyclic Ring Complex

[0079] In one embodiment, the pentaaza macrocyclic ring complex corresponds to the complex of Formula (I):



5 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

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;

U, together with the adjacent carbon atoms of the macrocycle, forms a fused

15 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.

[0080] As noted above in connection with the pentaaza macrocyclic ring complex of Formula (I), M is Mn²⁺ or Mn³⁺. In one particular embodiment in which the pentaaza macrocyclic ring complex corresponds to Formula (I), M is Mn²⁺. In another particular embodiment in which the pentaaza macrocyclic ring complex corresponds to Formula (I), M is Mn³⁺.

[0081] In the embodiments in which one or more of R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R₆, R'₆, R₇, R₈, R₉, R'₉, and R₁₀ are hydrocarbyl, for example, suitable hydrocarbyl moieties include, but are not limited to alkenyl, alkenylcycloalkenyl, alkenylcycloalkyl, alkyl, alkylcycloalkenyl, alkylcycloalkyl, alkynyl, aralkyl, aryl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, and aralkyl. In one embodiment, 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, or heterocyclyl. More preferably in this embodiment, R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R₆, R'₆, R₇, R₈, R₉, R'₉, and R₁₀ are independently hydrogen or lower alkyl (e.g., C₁-C₆ alkyl, more typically C₁-C₄ alkyl). Thus, for example, R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R₆, R'₆, R₇, R₈, R₉, R'₉, and R₁₀ may be independently hydrogen, methyl, ethyl, propyl, or butyl (straight, branched, or cyclic). In

one preferred embodiment, R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R₆, R'₆, R₇, R₈, R₉, R'₉, and R₁₀ are independently hydrogen or methyl.

[0082] In one preferred embodiment in which the pentaaza macrocyclic ring complex corresponds to Formula (I), R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R₇, R₈, R₉, R'₉, and R₁₀ are each hydrogen and one of R₆ and R'₆ is hydrogen and the other of R₆ and R'₆ is methyl. In this embodiment, for example, R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R₆, R₇, R₈, R₉, R'₉, and R₁₀ may each be hydrogen while R'₆ is methyl. Alternatively, for example, R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R'₆, R₇, R₈, R₉, R'₉, and R₁₀ may each be hydrogen while R₆ is methyl. In another preferred embodiment in which the pentaaza macrocyclic ring complex corresponds to Formula (I), R₁, R₃, R₄, R₅, R'₅, R'₆, R₇, R₈, and R₁₀ are each hydrogen, one of R₂ and R'₂ is hydrogen and the other of R₂ and R'₂ is methyl, and one of R₉ and R'₉ is hydrogen and the other of R₉ and R'₉ is methyl. In this embodiment, for example, R₁, R'₂, R₃, R₄, R₅, R'₅, R₇, R₈, R₉, and R₁₀ may each be hydrogen while R₂ and R'₉ are methyl. Alternatively, for example, R₁, R₂, R₃, R₄, R₅, R'₅, R₇, R₈, R'₉, and R₁₀ may each be hydrogen while R'₂ and R₉ are methyl. In another embodiment in which the pentaaza macrocyclic ring complex corresponds to Formula (I), R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R₆, R'₆, R₇, R₈, R₉, R'₉, and R₁₀ are each hydrogen.

[0083] In certain embodiments the U and V moieties are independently substituted or unsubstituted fused cycloalkyl moieties having 3 to 20 ring carbon atoms, more preferably 4 to 10 ring carbon atoms. In a particular embodiment, the U and V moieties are each trans-cyclohexanyl fused rings.

[0084] In certain embodiments the W moiety is a substituted or unsubstituted fused heteroaromatic moiety. In a particular embodiment, the W moiety is a substituted or unsubstituted fused pyridino moiety. Where W is a substituted fused pyridino moiety, for example, the W moiety is typically substituted with a hydrocarbyl or substituted hydrocarbyl moiety (e.g., alkyl, substituted alkyl) at the ring carbon atom positioned para to the nitrogen atom of the heterocycle. In a one preferred embodiment, the W moiety is an unsubstituted fused pyridino moiety.

[0085] As noted above, X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof (for example benzoic acid or benzoate anion, phenol or phenoxide anion, alcohol or alkoxide anion). For example, X and Y may be selected

- from the group consisting of halo, 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, among other possibilities.
- In one embodiment, X and Y if present, are independently selected from the group consisting of halo, nitrate, and bicarbonate ligands. For example, in this embodiment, X and Y, if present, are halo ligands, such as chloro ligands.

[0086] Furthermore, in one embodiment 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 $(=O)$;
 5 and
 each X_4 is independently hydrogen or together with X_3 is $(=O)$.

[0087] In yet another embodiment, 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
 10 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} .

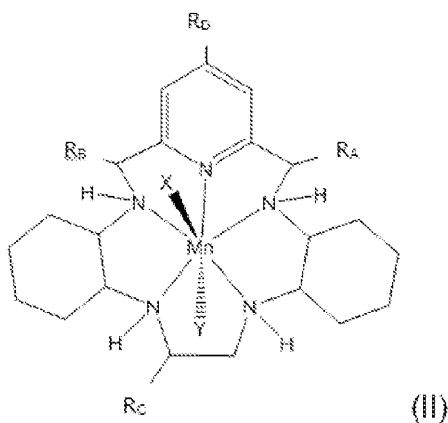
[0088] In the pentaaza macrocyclic ring complex corresponding to
 Formula (I), Z is a counterion (e.g., a charge-neutralizing anion), wherein n is an integer
 from 0 to 3. In general, Z may correspond to counterions of the moieties recited above
 15 in connection for X and Y.

[0089] In combination, among certain preferred embodiments are pentaaza
 macrocyclic ring complexes corresponding to Formula (I) 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
 20 hydrogen or lower alkyl;
 U and V are each trans-cyclohexanyl fused rings;
 W is a substituted or unsubstituted fused pyridino moiety;
 X and Y are ligands; and
 Z, if present, is a charge-neutralizing anion.

25 [0090] More preferably in these embodiments, M is Mn^{2+} ; 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 or methyl; U and V
 are each trans-cyclohexanyl fused rings; W is an unsubstituted fused pyridino moiety;
 and X and Y are independently halo ligands (e.g., fluoro, chloro, bromo, iodo). Z, if
 present, may be a halide anion (e.g., fluoride, chloride, bromide, iodide).

[0091] In yet another embodiment, the pentaaza macrocyclic ring complex is represented by Formula (II) below:



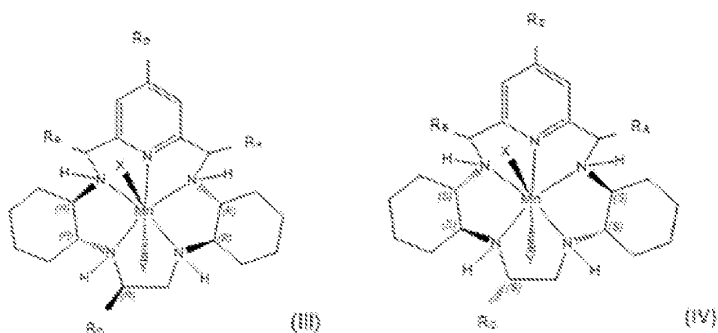
5 wherein

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

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

15 alkyl.

[0092] Furthermore, in one embodiment, the pentaaza macrocyclic ring complex is represented by Formula (III) or Formula (IV):

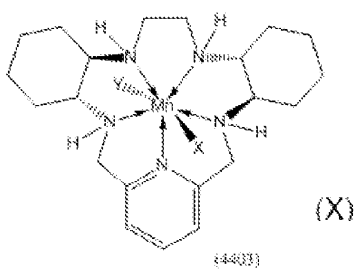
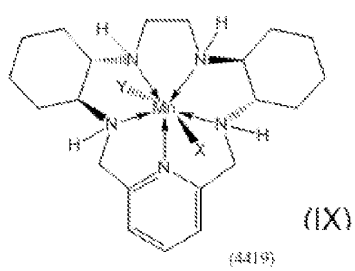
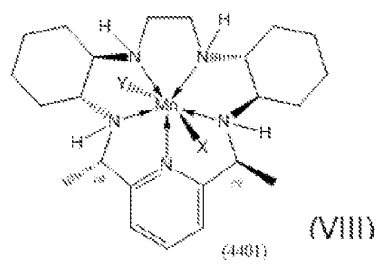
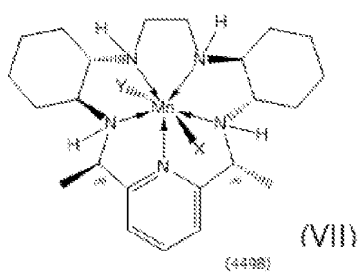
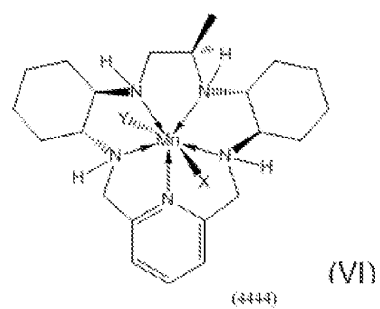
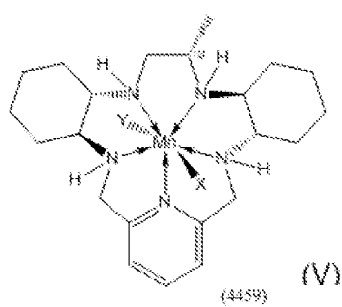


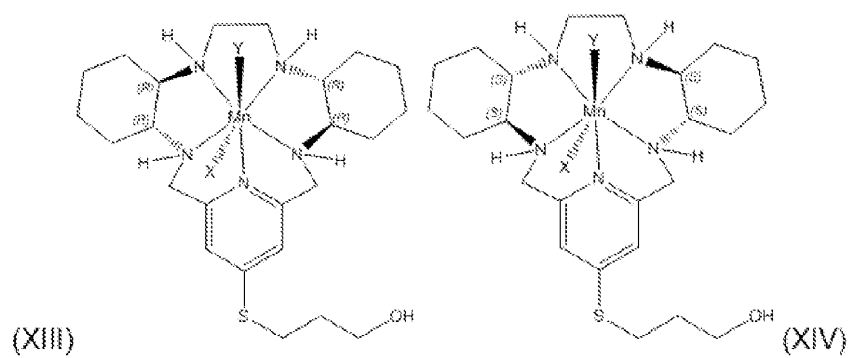
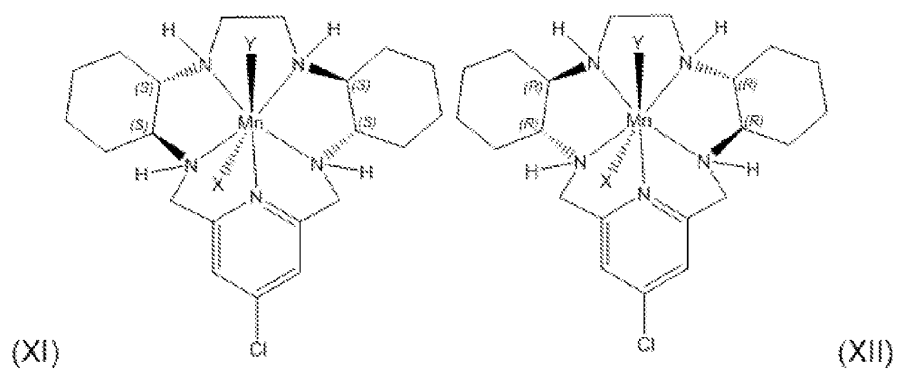
wherein

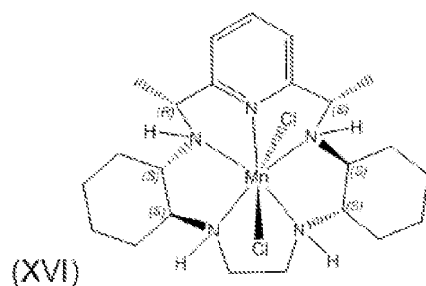
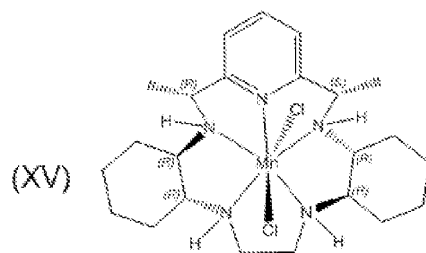
X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and

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.

[0093] In yet another embodiment, the pentaaza macrocyclic ring complex is a compound represented by a formula selected from the group consisting of Formulae (V)-(XVI):

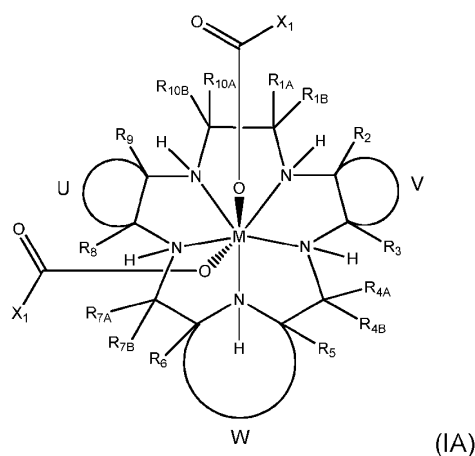






[0094] In one embodiment, X and Y in any of the formulae herein are
 5 independently selected from the group consisting of fluoro, chloro, bromo and iodo
 anions. In yet another embodiment, X and Y in any of the formulae herein are
 independently selected from the group consisting of alkyl carboxylates, aryl
 carboxylates and arylalkyl carboxylates. In yet another embodiment, X and Y in any of
 the formulae herein are independently amino acids.

10 [0095] In one embodiment, the pentaaza macrocyclic ring complex has the
 following Formula (IA):



wherein

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

5 R_{1A} , R_{1B} , R_2 , R_3 , R_{4A} , R_{4B} , R_5 , R_6 , R_{7A} , R_{7B} , R_8 , R_9 , R_{10A} , and R_{10B} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety independently selected from the group consisting of $-OR_{11}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{11}$, $-C(=O)NR_{11}R_{12}$, $-SR_{11}$, $-SOR_{11}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$, $-N(OR_{11})(R_{12})$, $-P(=O)(OR_{11})(OR_{12})$, $-P(=O)(OR_{11})(R_{12})$, and $-OP(=O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are

10 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;

15 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

20 part of the heterocycle and the macrocycle and R_5 and R_6 attached to the carbon

atoms which are both part of the heterocycle and the macrocycle are absent;
wherein

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 or alkyl;

5 each X_3 is independently hydrogen, hydroxyl, alkyl, amino, $-X_5C(=O)R_{13}$ where X_5 is NH or O, and R_{13} is C_1 - C_{18} alkyl, substituted or unsubstituted aryl or C_1 - C_{18} aralkyl, or $-OR_{14}$, where R_{14} is C_1 - C_{18} alkyl, substituted or unsubstituted aryl or C_1 - C_{18} aralkyl, or together with X_4 is $(=O)$;

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

10 the bonds between the transition metal M and the macrocyclic nitrogen atoms and the bonds between the transition metal M and the oxygen atoms of the axial ligands $-OC(=O)X_1$ are coordinate covalent bonds.

[0096] In one embodiment, within Formula (IA), and groups contained therein, in one group of compounds X_1 is $-C(-X_2)(-X_3)(-X_4)$ and each X_2 , X_3 , and X_4 , in
15 combination, corresponds to any of the combinations identified in the following table:

Combination	X_2	X_3	X_4
1	Ph	H	H
2	Ph	OH	H
3	Ph	NH ₂	H
4	Ph	=O (X_3 and X_4 in combination)	
5	Ph	CH ₃	H
6	CH ₃	H	H
7	CH ₃	OH	H
8	CH ₃	NH ₂	H
9	CH ₃	=O (X_3 and X_4 in combination)	

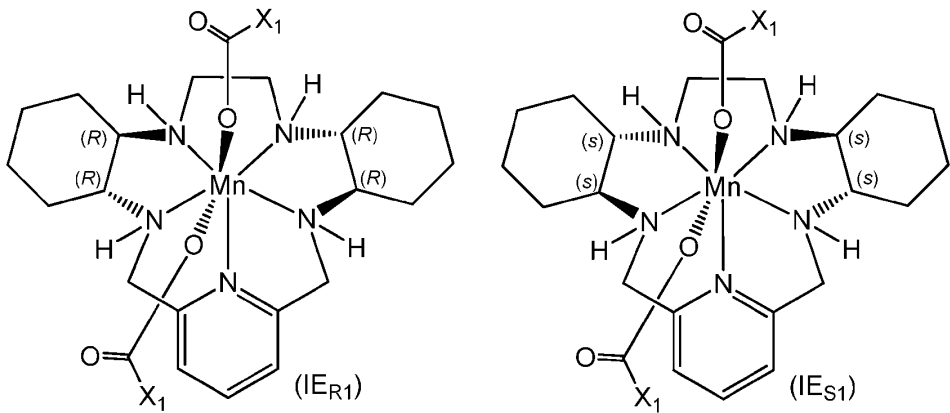
[0097] Furthermore, within embodiment (IA), and groups contained therein, in one group of compounds X_1 is $C(-X_2)(-X_3)(-X_4)$, and X_3 is $-X_5C(=O)R_{13}$, such that the combinations of X_2 , X_3 and X_4 include any of the combinations identified in the following table:

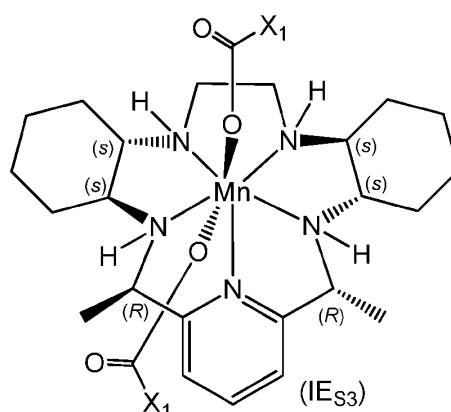
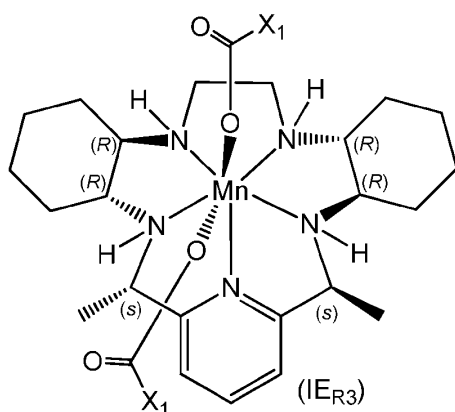
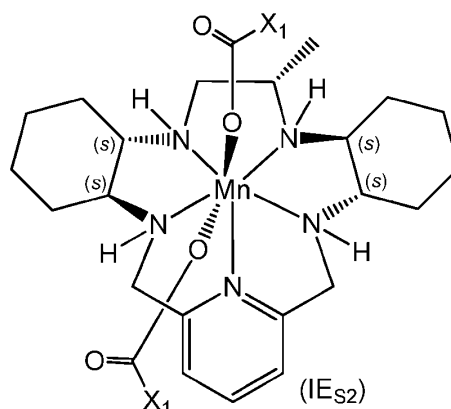
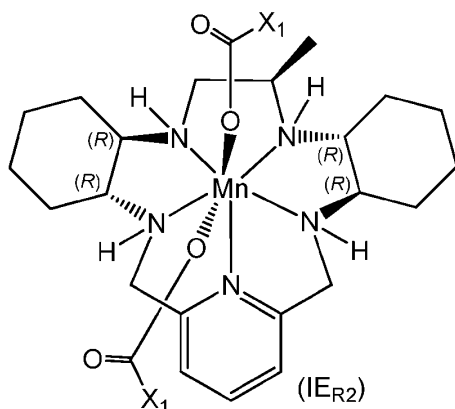
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Combination	X_2	X_3	X_4
1	Ph	$NHC(=O)R_{13}$	H
2	Ph	$OC(=O)R_{13}$	H
3	CH_3	$NHC(=O)R_{13}$	H
4	CH_3	$OC(=O)R_{13}$	H

where R_{13} is C_1 - C_{18} alkyl, substituted or unsubstituted aryl or C_1 - C_{18} aralkyl, or -
 OR_{14} , where R_{14} is C_1 - C_{18} alkyl, substituted or unsubstituted aryl or C_1 - C_{18} aralkyl.

[0098] In one embodiment, the pentaaza macrocyclic ring complex
10 corresponding to Formula (IA) is one of the complexes Formula (IE), such as (IE_{R1}),
(IE_{S1}), (IE_{R2}), (IE_{S2}), (IE_{R3}), or (IE_{S3}):





5

wherein

M is Mn⁺² or Mn⁺³;each X₁ is independently substituted or unsubstituted phenyl or -C(X₂)(X₃)(X₄);

each X₂ is independently substituted or unsubstituted phenyl, methyl, ethyl, or propyl;

10

each X₃ is independently hydrogen, hydroxyl, methyl, ethyl, propyl, amino, or together with X₄ is =O;

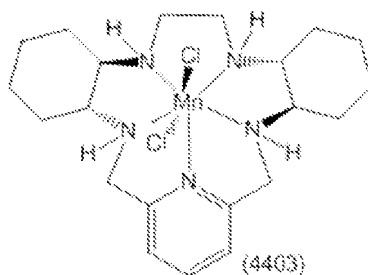
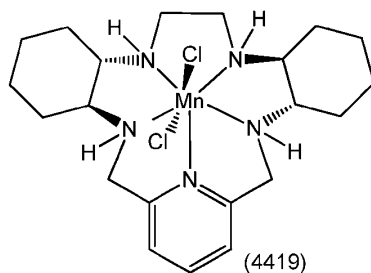
each X₄ is independently hydrogen or together with X₃ is =O; and

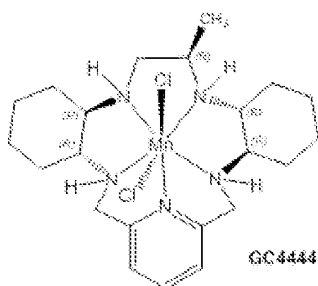
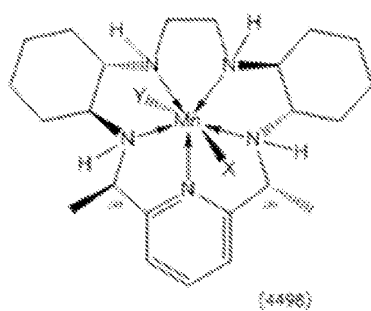
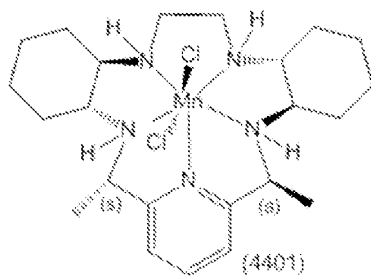
the bonds between the manganese and the macrocyclic nitrogen atoms and the bonds between the manganese and the oxygen atoms of the axial ligands $-\text{OC}(\text{O})\text{X}_1$ are coordinate covalent bonds.

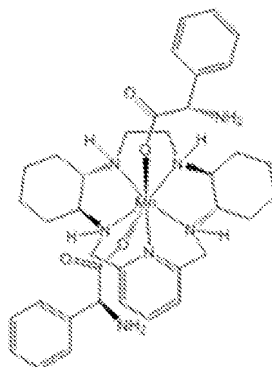
[0099] In one embodiment, each X_1 is $-\text{C}(\text{X}_2)(\text{X}_3)(\text{X}_4)$ and each $-\text{C}(\text{X}_2)(\text{X}_3)(\text{X}_4)$ corresponds to any of combinations 1 to 9 appearing in the table for Formula (IA) above.

[00100] In yet another embodiment, the X and Y in pentaaza macrocyclic ring complex of Formula (I) correspond to the ligands in Formulas (IA) or (IE). For example, X and Y in the complex of Formula (I) may correspond to $-\text{O}-\text{C}(\text{O})-\text{X}_1$, where X_1 is as defined for the complex of Formula (IA) and (IE) above.

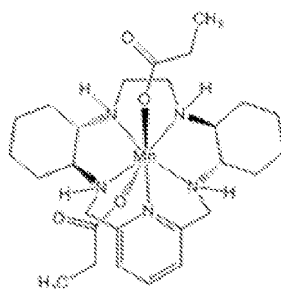
[00101] In one embodiment, the pentaaza macrocyclic ring complexes corresponding to Formula (I) (e.g., of Formula (I) or any of the subsets of Formula (I) corresponding to Formula (II)-(XIV), (IA) and (IE)), can comprise any of the following structures:





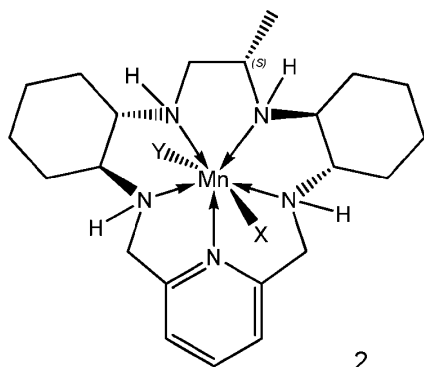


GC4702

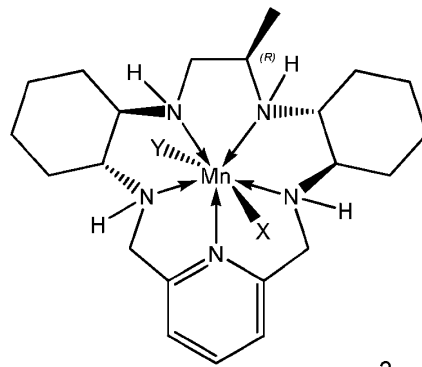


GC4711

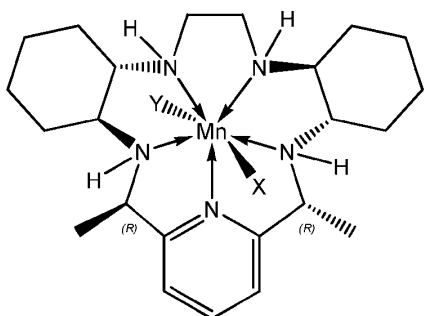
- 5 [00102] In one embodiment, the pentaaza macrocyclic ring complexes for use in the methods and compositions described herein include those corresponding to Formulae (2), (3), (4), (5), (6), and (7):



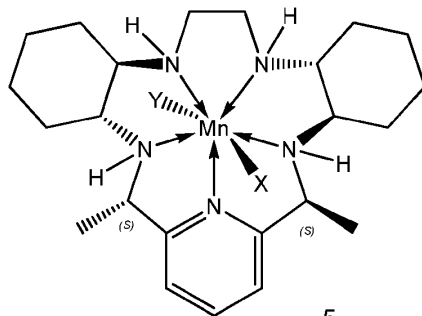
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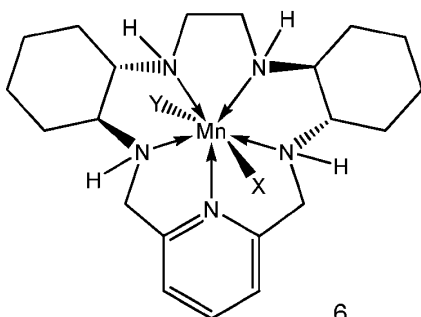
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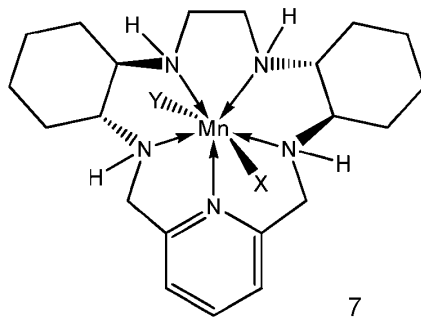
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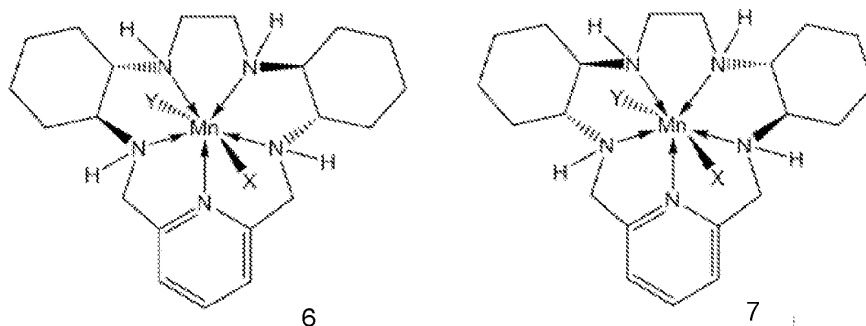
6



7

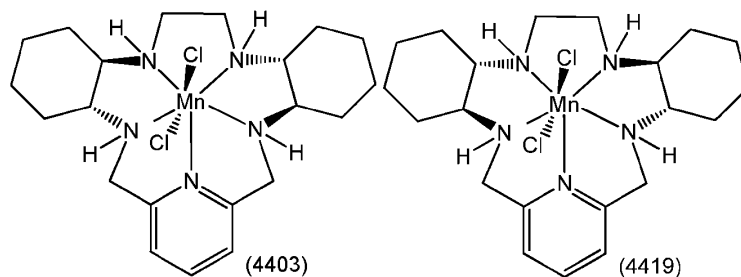
wherein X and Y in each of Formulae (2), (3), (4), (5), (6), and (7) are independently ligands. For example, according to one embodiment, the pentaaza macrocyclic ring complex for use in the methods and compositions described herein include those corresponding to Formulae (2), (3), (4), (5), (6), and (7) with X and Y in each of these formulae being halo, such as chloro. Alternatively, X and Y may be ligands other than chloro, such as any of the ligands described above.

[00103] In another embodiment, the pentaaza macrocyclic ring complex corresponds to Formula (6) or Formula (7):

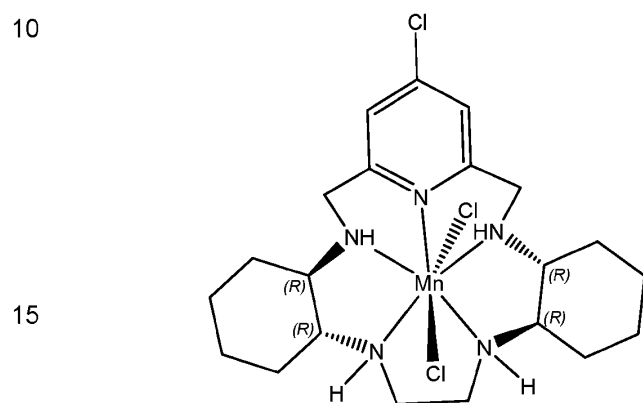
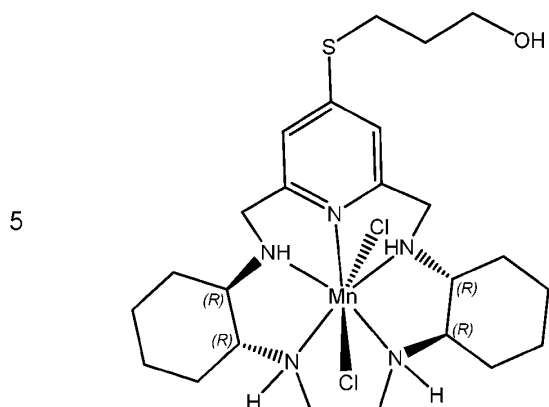


[00104] The chemical structures of 6 (such as the dichloro complex form described, for example, in Riley, D.P., Schall, O.F., 2007, *Advances in Inorganic Chemistry*, 59: 233-263) and of 7 herein (such as the dichloro complex form of 7), are identical except that they possess mirror image chirality; that is, the enantiomeric structures are non-superimposable.

[00105] For example, the pentaaza macrocyclic ring complex may correspond to at least one of the complexes below:



[00106] In yet another embodiment, the pentaaza macrocyclic ring complex may correspond to at least one of the complexes below, and/or an enantiomer thereof:



[00107] In one embodiment, the enantiomeric purity of the pentaaza
20 macrocyclic ring complex is greater than 95%, more preferably greater than 98%, more
preferably greater than 99%, and most preferably greater than 99.5%. As used herein,
the term “enantiomeric purity” refers to the amount of a compound having the depicted
absolute stereochemistry, expressed as a percentage of the total amount of the
depicted compound and its enantiomer. In one embodiment, the diastereomeric purity
25 of the pentaaza macrocyclic ring complex is greater than 98%, more preferably greater
than 99%, and most preferably greater than 99.5%. As used herein, the term
“diastereomeric purity” refers to the amount of a compound having the depicted
absolute stereochemistry, expressed as a percentage of the total amount of the

depicted compound and its diastereomers. Methods for determining diastereomeric and enantiomeric purity are well-known in the art. Diastereomeric purity can be determined by any analytical method capable of quantitatively distinguishing between a compound and its diastereomers, such as high performance liquid chromatography (HPLC).

5 Similarly, enantiomeric purity can be determined by any analytical method capable of quantitatively distinguishing between a compound and its enantiomer. Examples of suitable analytical methods for determining enantiomeric purity include, without limitation, optical rotation of plane-polarized light using a polarimeter, and HPLC using a chiral column packing material.

10 [00108] In one embodiment, a therapeutically effective amount of the pentaaza macrocyclic ring complex may be an amount sufficient to provide a peak plasma concentration of at least 0.1 μM when administered to a patient. For example, in one embodiment, the pentaaza macrocyclic ring complex may be administered in an amount sufficient to provide a peak plasma concentration of at least 1 μM when administered to a patient. In yet another embodiment, the pentaaza macrocyclic ring complex may be administered in an amount sufficient to provide a peak plasma concentration of at least 10 μM when administered to a patient. Generally, the pentaaza macrocyclic ring complex will not be administered in an amount that would provide a peak plasma concentration greater than 40 μM when administered to a patient. For example, the pentaaza macrocyclic ring complex may be administered in an amount sufficient to provide a peak plasma concentration in the range of from 0.1 μM to 40 μM in a patient. As another example, the pentaaza macrocyclic ring complex may be administered in an amount sufficient to provide a peak plasma concentration in the range of from 0.5 μM to 20 μM in a patient. As another example, the pentaaza macrocyclic ring complex may be administered in an amount sufficient to provide a peak plasma concentration in the range of from 1 μM to 10 μM in a patient.

[00109] In yet another embodiment, a dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be at least 0.1 mg/kg, such as at least 0.2 mg/kg. For example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be at least 0.5 mg/kg. As another example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be at least 1 mg/kg. In another example, the pentaaza macrocyclic compound that is administered per kg body weight

may be at least 2 mg/kg, such as at least 3 mg/kg, and even at least about 15 mg/kg, such as at least 24 mg/kg and even at least 40 mg/kg. Generally, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient will not exceed 1000 mg/kg. For example the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be in the range of from 0.1 to 1000 mg/kg, such as from 0.2 mg/kg to 40 mg/kg, such as 0.2 mg/kg to 24 mg/kg, and even 0.2 mg/kg to 10 mg/kg. As another example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight may be in a range of from 1 mg/kg to 1000 mg/kg, such as from 3 mg/kg to 1000 mg/kg, and even from 5 mg/kg to 1000 mg/kg, such as 10 mg/kg to 1000 mg/kg. As another example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight may be in a range of from 2 mg/kg to 15 mg/kg. As yet another example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight may be in a range of from 3 mg/kg to 10 mg/kg. As another example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be in the range of from 0.5 to 5 mg/kg. As yet a further example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be in the range of from 1 to 5 mg/kg.

[00110] In one embodiment, the dosages and/or plasma concentrations discussed above may be particularly suitable for the pentaaza macrocyclic ring complex corresponding to GC4419, although they may also be suitable for other pentaaza macrocyclic ring complexes. In addition, one of ordinary skill in the art would recognize how to adjust the dosages and/or plasma concentrations based on factors such as the molecular weight and/or activity of the particular compound being used. For example, for a pentaaza macrocyclic ring complex having an activity twice that of GC4419, the dosage and/or plasma concentration may be halved, or for a pentaaza macrocyclic ring complex having a higher molecular weight than GC4419, a correspondingly higher dosage may be used.

[00111] The dosing schedule of the pentaaza macrocyclic ring complex can similarly be selected according to the intended treatment. For example, in one embodiment, a suitable dosing schedule can comprise dosing a patient at least once per week, such as at least 2, 3, 4, 5, 6 or 7 days per week (e.g., daily), during a course of treatment. As another example, in one embodiment, the dosing may be at least once

a day (qd), or even at least twice a day (bid). In one embodiment, the course of treatment with the pentaaza macrocyclic ring complex may last at least as long as a course of treatment with radiation therapy, and may even exceed the duration during which the radiation therapy is provided. The course of therapy with the pentaaza
5 macrocyclic ring complex may also start on the same date as treatment with the radiation therapy, or may start sometime after initial dosing with the radiation therapy. For example, in one embodiment, for radiation therapy that is administered for a course of therapy lasting at least a day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, a month, two months, three months, four months,
10 five months, six months, the pentaaza macrocyclic ring complex may be administered for a course of therapy lasting at least at least a day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, a month, two months, three months, four months, five months, six months.

METHODS OF ADMINISTRATION

15 [00112] In one embodiment, the pentaaza macrocyclic ring complex can generally be administered according to therapeutic protocols that may be known for these agents. For example, the administration can be varied depending on the disease being treated and the effects of pentaaza macrocyclic ring complex on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols
20 (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

[00113] According to certain embodiments, the pentaaza macrocyclic ring complex can be administered with an anti-cancer therapeutic agent, such as a
25 chemotherapeutic agent. In general, where a therapy is provided with an anti-cancer therapeutic agent, the pentaaza macrocyclic ring complex and anti-cancer therapeutic agent do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, the pentaaza macrocyclic ring complex
30 may be administered orally to generate and maintain good blood levels thereof, while the optional anti-cancer therapeutic agent may be administered intravenously or via transfusion, or vice versa. The mode of administration may include, where possible, in

the same pharmaceutical composition, or in separate pharmaceutical compositions (e.g., two or three separate compositions). Furthermore, once the initial administration has been made, then based upon the observed effects, the dosage, modes of administration and times of administration can be modified.

5 [00114] The particular choice of pentaaza macrocyclic ring complex, and optionally the anti-cancer therapeutic agent and other related therapies (such as radiation, immunotherapy, or other chemotherapies), will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

10 [00115] Thus, in accordance with experience and knowledge, the practicing physician may modify each protocol for the administration of a component of the treatment according to the individual patient's needs, as the treatment proceeds.

 [00116] The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more
15 definite signs such as the risk of carcinogenesis, radiation exposure history, relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed.
20 Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

 [00117] The products of which any therapeutic composition herein are composed may be administered simultaneously, separately or spaced out over a period of time so as to obtain the maximum efficacy of the combination; it being possible for
25 each administration to vary in its duration from a rapid administration to a relatively continuous perfusion of either component (in separate formulations or in a single formulation). As a result, for the purposes of the present disclosure, the combinations are not exclusively limited to those which are obtained by physical association of the constituents, but also to those which permit a separate administration, which can be
30 simultaneous or spaced out over a period of time.

 [00118] Accordingly, administration of the components described herein can occur as a single event or over a time course of treatment. For example, the pentaaza

macrocyclic ring complex (and optional anti-cancer therapeutic agent) can be administered (simultaneously or in sequence) hourly (e.g., every hour, every two hours, every three hours, every four hours, every five hours, every six hours, and so on), daily, weekly, bi-weekly, or monthly. For treatment of acute conditions, the time course of treatment may be at least several hours or days. Certain conditions could extend treatment from several days to several weeks. For example, treatment could extend over one week, two weeks, or three weeks. For more chronic conditions, treatment could extend from several weeks to several months, a year or more, or the lifetime of the patient in need of such treatment. Alternatively, the compounds and agents can be administered hourly, daily, weekly, bi-weekly, or monthly, for a period of several weeks, months, years, or over the lifetime of the patient as a prophylactic measure.

[00119] The dose or amount of pharmaceutical compositions including the pentaaza macrocyclic ring complex (and optionally the anti-cancer therapeutic agent) administered to the patient should be an effective amount for the intended purpose, e.g., reducing the likelihood of cancer and increasing lifespan in the patient. Generally speaking, the effective amount of the composition administered can vary according to a variety of factors such as, for example, the age, weight, sex, diet, route of administration, and the medical condition of the patient in need of the treatment. Specifically preferred doses are discussed more fully herein. It will be understood, however, that the total daily usage of the compositions described herein will be decided by the attending physician or veterinarian within the scope of sound medical judgment.

[00120] According to certain embodiments, the pentaaza macrocyclic ring complex can be administered in an effective dosage amount, and for a course of therapy having a duration sufficient to increase the lifespan of a mammalian subject over the lifespan that the same mammalian subject would have, or would on average be expected to have, in the absence of such administration. For example, according to certain embodiments, the administration may be for only a fraction of the mammalian subject's lifespan, to provide protective effects that are sufficient to increase lifespan even after administration of the pentaaza macrocyclic ring complex has ceased, and/or even in a case of start of administration close to the end of the mammalian subject's

natural lifespan. According to one embodiment, a method of increasing lifespan in a mammalian subject comprises administering the pentaaza macrocyclic ring complex to the mammalian subject for at least 1 month, at least 3 months, at least 6 months, at least 1 year, at least 3 years, at least 5 years and/or at least 1 decade. According to one embodiment, the method of increasing lifespan in the mammalian subject comprises administering the pentaaza macrocyclic ring complex to the mammalian subject for no more than 2 decades, no more than 1 decade, no more than 5 yrs, no more than 3 years, no more than 1 year, no more than 6 months, no more than 3 months, and/or no more than 1 month. According to another embodiment, the method of increasing lifespan in the mammalian subject comprises administering the pentaaza macrocyclic ring complex to the mammalian subject only in first decade of life, in the second decade of life, in the third decade of life, in the fourth decade of life, in the fifth decade of life, in the sixth decade of life, in the seventh decade of life and/or in the eighth decade of life, or in a combination thereof, such as in at least a portion of one or more of the decades of the subject's life. According to another embodiment, the method of increasing lifespan in the mammalian subject comprises administering the pentaaza macrocyclic ring complex to the mammalian subject twice per day, once per day, every other day, weekly, bi-weekly, monthly, and/or bi-monthly.

[00121] The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound(s) employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound(s) employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound(s) employed and like factors well known in the medical and/or veterinary arts. If desired, the effective daily doses may be divided into multiple doses for purposes of administration. Consequently, single dose compositions may contain such amounts or submultiples to make up the daily dose.

[00122] In one embodiment, suitable or preferred doses for each of the components are employed in the methods or included in the compositions described herein. Preferred dosages for the pentaaza macrocyclic ring complex, for instance, may be within the range of 10 to 500 mg per patient per day. However, the dosage may vary depending on the dosing schedule, which can be adjusted as necessary to

achieve the desired therapeutic effect. It should be noted that the ranges of effective doses provided herein are not intended to limit the disclosure and represent exemplary dose ranges. The most preferred dosage will be tailored to the individual subject, taking into account, among other things, the particular combinations
5 employed, and the patient's age, sex, weight, physical condition, diet, *etc.*, as is understood and determinable by one of ordinary skill in the art without undue experimentation.

Reduction of Carcinogenesis

[00123] In general, any subject that may benefit from reduced risk of
10 carcinogenesis and/or increased lifespan, such as a subject that is likely to develop a cancer or other proliferative disorder due to exposure to therapeutic or non-therapeutic radiation, may be treated using the compositions and methods of the present disclosure. Subjects receiving treatment according to the methods described herein are mammalian subjects, and typically human patients. Other mammals that
15 may be treated according to the present disclosure include companion animals such as dogs and cats, farm animals such as cows, horses, and swine, as well more exotic animals (*e.g.*, those found in zoos or nature preserves). In one embodiment of the disclosure, a method is provided to reduce the likelihood of development of cancerous tumors, particularly solid tumors.

20 [00124] Cancer and tumors generally refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. By means of treatments of the present disclosure, the likelihood of developing cancers and tumors can be reduced. Examples of cancers and tumors for which the risk may be reduced can include tumors of the breast, heart, lung, small intestine, colon, spleen,
25 kidney, bladder, head and neck, ovary, prostate, brain, pancreas, skin, bone, bone marrow, blood, thymus, uterus, testicles, cervix, and liver.

[00125] In one embodiment, the tumor or cancer is chosen from adenoma, angio-sarcoma, astrocytoma, epithelial carcinoma, germinoma, glioblastoma, glioma, hamartoma, hemangioendothelioma, hemangiosarcoma, hematoma, hepato-
30 blastoma, leukemia, lymphoma, medulloblastoma, melanoma, neuroblastoma, osteosarcoma, retinoblastoma, rhabdomyosarcoma, sarcoma, and teratoma. The tumor can be chosen from acral lentiginous melanoma, actinic keratoses,

adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, Bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangio-carcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epithelioid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangioblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma, nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudo-sarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

[00126] Thus, for example, the present disclosure may provide methods for reducing the likelihood of developing a variety of cancers, including, but not limited to, the following: carcinoma including that of the bladder (including accelerated and metastatic bladder cancer), breast, colon (including colorectal cancer), kidney, liver, lung (including small and non-small cell lung cancer and lung adenocarcinoma), ovary, prostate, testes, genitourinary tract, lymphatic system, rectum, larynx, pancreas (including exocrine pancreatic carcinoma), esophagus, stomach, gall bladder, cervix, thyroid, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, histiocytic lymphoma, and Burkett's lymphoma; hematopoietic tumors of

myeloid lineage including acute and chronic myelogenous leukemias, myelodysplastic syndrome, myeloid leukemia, and promyelocytic leukemia; tumors of the central and peripheral nervous system including astrocytoma, neuroblastoma, glioma, and schwannomas; tumors of mesenchymal origin including fibrosarcoma,
 5 rhabdomyosarcoma, and osteosarcoma; and other tumors including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer, and teratocarcinoma.

[00127] For example, particular leukemias for which the risk can be reduced include, but are not limited to, acute nonlymphocytic leukemia, chronic lymphocytic
 10 leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemiac leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia,
 15 histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia,
 20 myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, and undifferentiated cell leukemia.

[00128] The risk of developing lymphomas can also be reduced with the methods described herein. Lymphomas are generally neoplastic transformations of cells
 25 that reside primarily in lymphoid tissue. Lymphomas are tumors of the immune system and generally are present as both T cell- and as B cell-associated disease. Among lymphomas, there are two major distinct groups: non-Hodgkin's lymphoma (NHL) and Hodgkin's disease. Bone marrow, lymph nodes, spleen and circulating cells, among others, may be involved. Treatment protocols include removal of bone marrow from the
 30 patient and purging it of tumor cells, often using antibodies directed against antigens present on the tumor cell type, followed by storage. The patient is then given a toxic dose of radiation or chemotherapy and the purged bone marrow is then re-infused in order to repopulate the patient's hematopoietic system.

[00129] Other hematological malignancies for which the risk can be reduced with the methods described herein include myelodysplastic syndromes (MDS), myeloproliferative syndromes (MPS) and myelomas, such as solitary myeloma and multiple myeloma. Multiple myeloma (also called plasma cell myeloma) involves the skeletal system and is characterized by multiple tumorous masses of neoplastic plasma cells scattered throughout that system. It may also spread to lymph nodes and other sites such as the skin. Solitary myeloma involves solitary lesions that tend to occur in the same locations as multiple myeloma.

[00130] In one embodiment, the methods and pharmaceutical compositions described herein are used to reduce the likelihood of developing a cancer that is any of breast cancer, melanoma, oral squamous cell carcinoma, lung cancer including non-small cell lung cancer, renal cell carcinoma, colorectal cancer, prostate cancer, brain cancer, spindle cell carcinoma, urothelial cancer, bladder cancer, colorectal cancer, head and neck cancers such as squamous cell carcinoma, and pancreatic cancer. According to yet another embodiment, the cancer for which the likelihood of risk is reduced is any one selected from the group consisting of breast cancer, prostate cancer, testicular cancer, glioma, glioblastoma, head and neck cancer, ovarian cancer, endometrial cancer, hepatocellular carcinoma, desmoid tumors, pancreatic carcinoma, melanoma, and renal cell carcinoma.

[00131] According to certain embodiments, the subject to whom the pentaaza macrocyclic ring complex is administered to reduce the risk of carcinogenesis is one that has or is suffering from any of the cancers or tumors described herein, and who has already, is currently, or is scheduled to receive radiation therapy to treat the cancer or tumor.

Pharmaceutical Formulations

[00132] Another aspect of the present disclosure relates to the pharmaceutical compositions comprising the pentaaza macrocyclic ring complex described herein, together with a pharmaceutically acceptable excipient. The pharmaceutical compositions include the pentaaza macrocyclic ring complex (e.g., those corresponding to Formula (I)), and optionally at least anti-cancer therapeutic agent, and combinations thereof, as discussed above, typically formulated as a pharmaceutical dosage form, optionally in combination with a pharmaceutically acceptable carrier, additive or

excipient. Pharmaceutical compositions according to the present disclosure may be used to reduce the risk of carcinogenesis and/or to increase lifespan of a subject.

[00133] The pharmaceutical compositions described herein can include both fixed and non-fixed combinations of one or more active ingredients. Fixed combinations are those in which the active ingredients, e.g., a pentaaza macrocyclic ring complex and an optional anti-cancer therapeutic agent, are administered to a patient simultaneously in the form of a single entity or dosage. Other active agents may also be administered as a part of the single entity or dosage, or may be separately administered. Non-fixed combinations are those in which the active ingredients, e.g., a pentaaza macrocyclic ring complex and an optional anti-cancer therapeutic agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the compounds in the body of the patient. The latter also applies to cocktail therapy, e.g., the administration of three or more active ingredients.

[00134] The above-described pentaaza macrocyclic ring complex may be dispersed in a pharmaceutically acceptable carrier prior to administration to the mammal. The carrier, also known in the art as an excipient, vehicle, auxiliary, adjuvant, or diluent, is typically a substance which is pharmaceutically inert, confers a suitable consistency or form to the composition, and does not diminish the efficacy of the compound. The carrier is generally considered to be "pharmaceutically or pharmacologically acceptable" if it does not produce an unacceptably adverse, allergic or other untoward reaction when administered to a mammal, especially a human.

[00135] The selection of a pharmaceutically acceptable carrier will also, in part, be a function of the route of administration. In general, the compositions of the described herein can be formulated for any route of administration so long as the blood circulation system is available via that route, and in accordance with the conventional route of administration. For example, suitable routes of administration include, but are not limited to, oral, parenteral (e.g., intravenous, intraarterial, subcutaneous, rectal, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intraperitoneal, or intrasternal), topical (nasal, transdermal, intraocular), intravesical, intrathecal, enteral, pulmonary, intralymphatic, intracavitary, vaginal, transurethral, intradermal, aural,

intramammary, buccal, orthotopic, intratracheal, intralesional, percutaneous, endoscopic, transmucosal, sublingual and intestinal administration.

[00136] Pharmaceutically acceptable carriers for use in the compositions of the present disclosure are well known to those of ordinary skill in the art and are selected based upon a number of factors: the particular compound(s) and agent(s) used, and its/their concentration, stability and intended bioavailability; the subject, its age, size and general condition; and the route of administration. Suitable nonaqueous, pharmaceutically-acceptable polar solvents include, but are not limited to, alcohols (e.g., a-glycerol formal, 6-glycerol formal, 1,3-butyleneglycol, aliphatic or aromatic alcohols having 2 to 30 carbon atoms such as methanol, ethanol, propanol, isopropanol, butanol, t-butanol, hexanol, octanol, amylene hydrate, benzyl alcohol, glycerin (glycerol), glycol, hexylene glycol, tetrahydrofurfuryl alcohol, lauryl alcohol, cetyl alcohol, or stearyl alcohol, fatty acid esters of fatty alcohols such as polyalkylene glycols (e.g., polypropylene glycol, polyethylene glycol), sorbitan, sucrose and cholesterol); amides (e.g., dimethylacetamide (DMA), benzyl benzoate DMA, dimethylformamide, N-(6-hydroxyethyl)-lactamide, N,N-dimethylacetamide amides, 2-pyrrolidinone, 1-methyl-2-pyrrolidinone, or polyvinylpyrrolidone); esters (e.g., 1-methyl-2-pyrrolidinone, 2-pyrrolidinone, acetate esters such as monoacetin, diacetin, and triacetin, aliphatic or aromatic esters such as ethyl caprylate or octanoate, alkyl oleate, benzyl benzoate, benzyl acetate, dimethylsulfoxide (DMSO), esters of glycerin such as mono, di-, or tri-glyceryl citrates or tartrates, ethyl benzoate, ethyl acetate, ethyl carbonate, ethyl lactate, ethyl oleate, fatty acid esters of sorbitan, fatty acid derived PEG esters, glyceryl monostearate, glyceride esters such as mono, di-, or tri-glycerides, fatty acid esters such as isopropyl myristate, fatty acid derived PEG esters such as PEG-hydroxyoleate and PEG-hydroxystearate, N-methyl pyrrolidinone, pluronic 60, polyoxyethylene sorbitol oleic polyester, polyoxyethylene sorbitan esters such as polyoxyethylene-sorbitan monooleate, polyoxyethylene-sorbitan monopalmitate, polyoxyethylene-sorbitan monolaurate, polyoxyethylene-sorbitan monostearate, and Polysorbate® 20, 40, 60 or 80 from ICI Americas, Wilmington, DE, polyvinylpyrrolidone, alkyleneoxy modified fatty acid esters such as polyoxyl 40 hydrogenated castor oil and polyoxyethylated castor oils (e.g., Cremophor® EL solution or Cremophor® RH 40 solution), saccharide fatty acid esters (i.e., the condensation product of a monosaccharide (e.g., pentoses such as ribose, ribulose, arabinose, xylose, lyxose and xylulose, hexoses such as glucose,

- fructose, galactose, mannose and sorbose, trioses, tetroses, heptoses, and octoses), disaccharide (e.g., sucrose, maltose, lactose and trehalose) or oligosaccharide or mixture thereof with a C₄ to C₂₂ fatty acid(s) (e.g., saturated fatty acids such as caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid and stearic acid, and
- 5 unsaturated fatty acids such as palmitoleic acid, oleic acid, elaidic acid, erucic acid and linoleic acid)), or steroidal esters); alkyl, aryl, or cyclic ethers having 2 to 30 carbon atoms (e.g., diethyl ether, tetrahydrofuran, dimethyl isosorbide, diethylene glycol monoethyl ether); glycofuro (tetrahydrofurfuryl alcohol polyethylene glycol ether); ketones having 3 to 30 carbon atoms (e.g., acetone, methyl ethyl ketone, methyl isobutyl
- 10 ketone); aliphatic, cycloaliphatic or aromatic hydrocarbons having 4 to 30 carbon atoms (e.g., benzene, cyclohexane, dichloromethane, dioxolanes, hexane, n-decane, n-dodecane, n-hexane, sulfolane, tetramethylenesulfon, tetramethylenesulfoxide, toluene, di methylsulfoxide (DMSO), or tetramethylenesulfoxide); oils of mineral, vegetable, animal, essential or synthetic origin (e.g., mineral oils such as aliphatic or wax-based
- 15 hydrocarbons, aromatic hydrocarbons, mixed aliphatic and aromatic based hydrocarbons, and refined paraffin oil, vegetable oils such as linseed, tung, safflower, soybean, castor, cottonseed, groundnut, rapeseed, coconut, palm, olive, corn, corn germ, sesame, persic and peanut oil and glycerides such as mono-, di- or triglycerides, animal oils such as fish, marine, sperm, cod-liver, haliver, squalene, squalane, and shark
- 20 liver oil, oleic oils, and polyoxyethylated castor oil); alkyl or aryl halides having 1 to 30 carbon atoms and optionally more than one halogen substituent; methylene chloride; monoethanolamine; petroleum benzin; trolamine; omega-3 polyunsaturated fatty acids (e.g., alpha-linolenic acid, eicosapentaenoic acid, docosapentaenoic acid, or docosahexaenoic acid); polyglycol ester of 12-hydroxystearic acid and polyethylene
- 25 glycol (Solutol® HS-15, from BASF, Ludwigshafen, Germany); polyoxyethylene glycerol; sodium laurate; sodium oleate; or sorbitan monooleate.

[00137] In some embodiments, oils or non-aqueous solvents may be employed in the formulations, e.g., to bring one or more of the compounds into solution, due to, for example, the presence of large lipophilic moieties. Alternatively,

30 emulsions, suspensions, or other preparations, for example, liposomal preparations, may be used. With respect to liposomal preparations, for example, any known methods for preparing liposomes may be used. See, for example, Bangham *et al.*, J. Mol. Biol, 23: 238-252 (1965) and Szoka *et al.*, Proc. Natl Acad. Sci 75: 4194-4198

(1978), incorporated herein by reference. Thus, in one embodiment, one or more of the compounds are administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines. Ligands may also be attached to the liposomes, for instance, to direct these compositions to particular sites of action.

[00138] Other pharmaceutically acceptable solvents for use in the pharmaceutical compositions described herein are well known to those of ordinary skill in the art, and are identified in The Chemotherapy Source Book (Williams & Wilkins Publishing), The Handbook of Pharmaceutical Excipients, (American Pharmaceutical Association, Washington, D.C., and The Pharmaceutical Society of Great Britain, London, England, 1968), Modern Pharmaceutics, (G. Banker *et al.*, eds., 3d ed.) (Marcel Dekker, Inc., New York, New York, 1995), The Pharmacological Basis of Therapeutics, (Goodman & Gilman, McGraw Hill Publishing), Pharmaceutical Dosage Forms, (H. Lieberman *et al.*, eds.) (Marcel Dekker, Inc., New York, New York, 1980), Remington's Pharmaceutical Sciences (A. Gennaro, ed., 19th ed.) (Mack Publishing, Easton, PA, 1995), The United States Pharmacopeia 24, The National Formulary 19, (National Publishing, Philadelphia, PA, 2000), and A.J. Spiegel *et al.*, Use of Nonaqueous Solvents in Parenteral Products, Journal of Pharmaceutical Sciences, Vol. 52, No. 10, pp. 917-927 (1963).

[00139] Formulations containing the pentaaza macrocyclic ring complex may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms such as, for instance, aerosols, capsules, creams, emulsions, foams, gels/jellies, lotions, ointments, pastes, powders, soaps, solutions, sprays, suppositories, suspensions, sustained-release formulations, tablets, tinctures, transdermal patches, and the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[00140] In one embodiment, a formulation is provided as a part of liquid dosage form, such as a sterile liquid dosage form suitable for injection. For example, the liquid form containing the pentaaza macrocyclic ring complex can be provided in combination with one or more further ingredients, such as edetate disodium (EDTA). In one embodiment, the liquid form can comprise EDTA in an amount suitable to act as a preservative and/or metal-chelating agent, such as an amount of about 0.025%. The

liquid form can further comprise water, and may also comprise a pH adjuster, such as sodium bicarbonate, for pH adjustment in the range of pH 5.5 to 7.0.

[00141] Formulations for certain pentaaza macrocyclic ring complexes are also described in, for example, in U.S. Patent Nos. 5,610,293, 5,637,578, 5,874,421, 5,976,498, 6,084,093, 6,180,620, 6,204,259, 6,214,817, 6,245,758, 6,395,725, and 6,525,041 (each of which is hereby incorporated herein by reference in its entirety).

[00142] The above-described pharmaceutical compositions including the pentaaza macrocyclic compound may additionally include one or more additional pharmaceutically active components. Suitable pharmaceutically active agents that may be included in the compositions according to aspects of the present invention include, for instance, antiemetics, anesthetics, antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatory agents, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's Disease agents, antibiotics, anti-depressants, and antiviral agents. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

[00143] In yet another embodiment, a kit may be provided that includes the pentaaza macrocyclic ring complex, and optionally the anti-cancer therapeutic agent, with instructions for administration to reduce the risk of carcinogenesis and/or to increase lifespan. For example, the kit may comprise a first vessel or container having therein a formulation comprising the pentaaza macrocyclic ring complex, such as an oral or injectable formulation of the pentaaza macrocyclic ring complex, and optionally a second vessel or container having therein a formulation comprising the anti-cancer therapeutic agent, such as an injectable formulation of anti-cancer therapeutic agent. The kit may further comprise a label or other instructions for administration of the active agents, recommended dosage amounts, durations and administration regimens, warnings, listing of possible drug-drug interactions, and other relevant instructions, such as a label instructing therapeutic regimens (*e.g.*, dosing, frequency of dosing, *etc.*) corresponding to any of those described herein.

Radiation Therapy

[00144] In one embodiment, the pentaaza macrocyclic ring complex can be administered in combination with radiation therapy, such as before, after or during radiation therapy, to reduce the risk of developing radiogenic cancers from such radiation therapy. According to further embodiments, the pentaaza macrocyclic ring complex can be administered long after a course of radiation therapy, such as to a mammalian subject whose cancer is in remission following radiation therapy.

[00145] In general, the temporal aspects of the administration of the pentaaza macrocyclic ring complex may depend for example, on the particular radiation therapy that is selected, or the type, nature, and/or duration of the radiation exposure. Other considerations may include the disease or disorder being treated and the severity of the disease or disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors. For example, the pentaaza macrocyclic ring complex may be administered in various embodiments before, during, and/or after the administration of the radiation therapy (e.g., before, during or after exposure to and/or before, during or after a course of radiation therapy comprising multiple exposures and/or doses). By way of another example, the pentaaza macrocyclic ring complex may be administered in various embodiments before, during, and/or after an exposure to radiation. In one embodiment, the radiation therapy can comprise any selected from the group consisting of gamma irradiation, proton therapy, heavy ion therapy, brachytherapy, radionuclide therapy, conformal radiation therapy, intensity modulated radiation therapy, stereotactic body radiation therapy, stereoablative radiation therapy, and gamma knife therapy, whether delivered as standard fractionation, hypofractionation, accelerated fractionation or decelerated fractionation and variations thereof.

[00146] In radiation therapy, a patient receives a dose or dose fraction of ionizing radiation to kill or control the growth of cancerous cells. The dose or dose fraction of radiation may be directed at a specific part of the body, and the beam of radiation may also be shaped according to a predetermined treatment regimen, to

reduce deleterious effects on parts of the body not afflicted with cancer. A typical course of radiation therapy may include one or a plurality of doses or dose fractions of radiation, which can be administered over the course of days, weeks and even months. A total “dose” of radiation given during a course of radiation therapy typically refers to
5 the amount of radiation a patient receives during the entire course of radiation therapy, which doses may be administered as dose “fractions” corresponding to multiple radiation exposures in the case where the total dose is administered over several sessions, with the sum of the fractions administered corresponding to the overall dose

[00147] In one embodiment, for example, the pentaaza macrocyclic ring
10 complex is administered to the patient prior to or simultaneous with the radiation exposure. In another embodiment, for example, the pentaaza macrocyclic ring complex is administered to the patient prior to, but not after, the radiation exposure. In yet another embodiment, the pentaaza macrocyclic ring complex is administered to the patient at least 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 180
15 minutes, 0.5 days, 1 day, 3 days, 5 days, one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, ten weeks, eleven weeks, twelve weeks, or longer, prior to the radiation exposure, such as an initial radiation exposure in a course of radiation treatment, or prior to another dose or dose fraction of radiation that is one of the doses or dose fractions of radiation in the course
20 of treatment. In still other embodiments, for example, the pentaaza macrocyclic ring complex is administered to the patient after the radiation exposure; thus, for example, the compound may be administered up to 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, or 180 minutes, 0.5 days, 1 day, 3 days, 5 days, one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine
25 weeks, ten weeks, eleven weeks, twelve weeks, or longer, after the radiation exposure, which may be a dose or dose fraction of radiation in a multi-dose course of radiation therapy, or may be the single or final dose or dose fraction of radiation in the radiation therapy.

[00148] In one embodiment, the pentaaza macrocyclic ring complex is
30 administered within a predetermined time period before or after a radiation exposure, such as a before or after a radiation dose or dose fraction. For example, the pentaaza macrocyclic ring complex may be administered within 1 week, 48 hours, 24 hours, 12 hours, 6, hours, 2 hours, 1 hour or even within 30 minutes of the patient receiving the

radiation exposure, such as the dose or dose fraction (either before or after the radiation exposure corresponding to the radiation dose or dose fraction). Other durations between the radiation exposure and administration of the compound may also be suitable.

5 [00149] In one embodiment, a course of radiation therapy includes a plurality of radiation doses or dose fractions given over a predetermined period of time, such as over the course of hours, weeks, days and even months, with the plural doses or dose fractions being either of the same magnitude or varying. That is, a course of radiation therapy can comprise the administration of a series of multiple doses or dose fractions
10 of radiation. In one embodiment, the pentaaza macrocyclic ring complex can be administered before one or more radiation doses or dose fractions in the series, such as before each radiation dose or dose fraction, or before some number of the radiation doses or dose fractions. In one embodiment, the pentaaza macrocyclic ring complex is administered within a predetermined duration before or after of each dose or dose
15 fraction, such as the predetermined duration discussed above. In another embodiment, the pentaaza macrocyclic ring complex is administered within a predetermined duration of time before or after only select doses or dose fractions.

 [00150] A suitable overall dose to provide during a course of therapy can be determined according to the type of treatment to be provided, the physical
20 characteristics of the patient and other factors, and the dose fractions that are to be provided can be similarly determined. In one embodiment, a dose fraction of radiation that is administered to a patient may be at least 1.8 Gy, such as at least 2 Gy, and even at least 3 Gy, such as at least 5 Gy, and even at least 6 Gy. In yet another embodiment, a dose fraction of radiation that is administered to a patient may be at
25 least 10 Gy, such as at least 12 Gy, and even at least 15 Gy, such as at least 18 Gy, and even at least 20 Gy, such as at least 24 Gy. In general, a dose fraction of radiation administered to a patient will not exceed 54 Gy. Furthermore, it should be noted that, in one embodiment, a dose fraction delivered to a subject may refer to an amount delivered to a specific target region of a subject, such as a target region of a tumor,
30 whereas other regions of the tumor or surrounding tissue may be exposed to more or less radiation than that specified by the nominal dose fraction amount.

[00151] For example, in one embodiment, the overall dose of radiation provided during the course of therapy may be provided via a hypofractionation radiotherapy scheme, which typically involves providing relatively high dose fractions administered over relatively fewer sessions, as compared to lower dose fraction schemes. Examples of such hypofractionation radiotherapy methods can include, but are not limited to, stereotactic radiosurgery (SRS), which typically refers to a single-fraction treatment directed to targets such as intracranial and spinal targets, as well as stereotactic body radiation therapy (SBRT), which typically refers to multifractional treatment of targets such as intracranial and spinal targets, and also extracranial targets such as lung, liver, head and neck, pancreas and prostate. As an example, in one embodiment of a hypofractionation radiotherapy scheme, the overall dose of radiation provided during the course of therapy may be divided into less than 10 fractions, such as less than 8 fractions, less than 6 fractions, less than 5 fractions, less than 4 fractions, less than 3 fractions, less than 2 fractions and may even be provided in just one administration (single fraction). For example, in one embodiment, the overall dose of radiation provided during the course of therapy may be divided into from 1 to 10 fractions, such as from 1 to 6 fractions, and even from 1 to 5 fractions, such as from 2 to 5 fractions or even 2 to 4 fractions. As yet another example, the hypofractionation radiotherapy scheme can comprise dividing the overall dose of radiation provided during the course of therapy into dose fractions that are at least 10% (1/10) of the overall dose provided during therapy, such as at least 12.5% (1/8) of the overall dose, at least 16% (~1/6) of the overall dose, at least 20% (1/5) of the overall dose, at least 25% (1/4) of the overall dose, at least 30% (1/3) of the overall dose, at least 50% of the overall dose, and/or at least 100% of the overall dose may be provided in a single administration (single fraction). For example, in one embodiment, the overall dose of radiation provided during the course of therapy may be divided into fractions that provide from 10% to 100% of the overall dose in each fraction, such as from 16% to 100% of the overall dose, and even from 20% to 100% of the overall dose, such as from 20% to 50% of the overall dose or even from 25% to 50% of the overall dose. For example a dose fraction size may be at least 5 Gy, such as at least 6 Gy, at least 8 Gy, at least 10 Gy, at least 12 Gy, and even at least 15 Gy, such as at least 18 Gy, and even at least 20 Gy, such as at least 24 Gy, and typically do not exceed 54 Gy, such as less than 40 Gy and even less than 30 Gy. In one embodiment, dose fraction sizes may be in the range of

from 5 Gy to 30 Gy, such as from 6 Gy to 28 Gy, and even from 8 Gy to 25 Gy.

Furthermore, in one embodiment, the dose fractions may be administered no more than three times per day, and even no more than twice per day, such as no more than once per day, on consecutive or non-consecutive days and/or some combination thereof, and
5 may be administered over a period of a few days and up to a few weeks, such as over a period of 1 to 15 days, 1 to 12 days, 1 to 10 days, 1 to 5 days, and even 1 to 3 days.

Typically, the dose fractions making up the overall course of therapy will be administered in no more than 20 days, no more than 15 days, no more than 10 days, no more than 5 days, and even no more than 3 days.

10 [00152] As yet another example, in one embodiment, the overall dose of radiation provided during the course of therapy may be provided via a radiotherapy scheme that provides relatively lower dose fractions administered over relatively more sessions, as compared to, e.g., hypofractionation schemes. Examples of such lower
15 dose fraction radiotherapy methods can include, but are not limited to, intensity-modulated radiation therapy (IMRT) and image guided radiation therapy (IGRT), which typically involve three-dimensional conformal therapy (3D-CRT) to match the administered radiation to a target volume. As an example, in one embodiment of such a radiotherapy scheme, the overall dose of radiation provided during the course of
20 therapy may be divided into at least 15 fractions, such as at least 18 fractions, at least 20 fractions, at least 22 fractions, at least 25 fractions, at least 28 fractions, at least 30 fractions, at least 32 fractions, at least 35 fractions, and even at least 38 fractions, although the total number of fractions will typically be less than 50, such as less than 45, and even less than 42. For example, in one embodiment, the overall dose of radiation provided during the course of therapy may be divided into from 15 to 38
25 fractions, such as from 20 to 38 fractions, and even from 20 to 35 fractions, such as from 25 to 35 fractions. As yet another example, the radiotherapy scheme can comprise dividing the overall dose of radiation provided during the course of therapy into dose fractions that are no more than 7% (1/15) of the overall dose provided during therapy, such as no more than 6% (1/18) of the overall dose, no more than 5% (1/20) of
30 the overall dose, no more than 4.5% (1/22) of the overall dose, no more than 4% (1/25) of the overall dose, no more than 3.6% (1/28) of the overall dose, no more than 3.3% (1/30) of the overall dose, no more than 3.1% (1/32) of the overall dose, no more than 2.8% of the overall dose (1/35), and even no more than 2.6% (1/38) of the overall dose.

For example, in one embodiment, the overall dose of radiation provided during the course of therapy may be divided into fractions that provide from 2.5% to 8% of the overall dose in each fraction, such as from 2.8% to 5% of the overall dose, and even from 2.8% to 4% of the overall dose. For example a dose fraction size may be less than 5 Gy, such as less than 4 Gy, less than 3.5 Gy, less than 3 Gy, less than 2.8 Gy, and even less than 2.5 Gy, such as less than 2.3 Gy, and even less than 2 Gy, such as less than 1.8 Gy, and typically is at least 0.5 Gy, such as at least 1 Gy and even at least 1.5 Gy. In one embodiment, dose fraction sizes may be in the range of from 1.5 Gy to 4.5 Gy, such as from 1.8 Gy to 3 Gy, and even from 2 Gy to 2.5 Gy. Furthermore, in one embodiment, the dose fractions may be administered no more than three times per day, and even no more than twice per day, such as no more than once per day, on consecutive or non-consecutive days, and/or a combination thereof (e.g., on consecutive weekdays), and in some embodiments may be administered over a period of a few days to a few weeks and even a few months, such as over a period of up to 3 weeks, up to 5 weeks, up to 6 weeks, up to 8 weeks and even up to 10 weeks, such as in a range of from 3 weeks to 10 weeks, or even in a range of from 5 weeks to 8 weeks. For example, the dose fractions making up the overall course of therapy can be administered in no more than 12 weeks, such as no more than 10 weeks and even no more than 8 weeks.

[00153] In yet another embodiment, the overall dose of radiation provided by the radiation scheme, whether in a relatively high dose fraction scheme or relatively low dose fraction scheme such as those described above, or other scheme, is selected to provide suitable treatment of the cancer. The overall dose may also be provided according to the specific dose fractionation scheme being administered, along with other factors. For example, in certain embodiments, a relatively larger overall dose may be administered as relatively smaller individual dose fractions. In one embodiment, the overall dose provided over the course of the therapy (i.e., the sum of the administered dose fractions), is at least 50 Gy, such as at least 55 Gy, at least 58 Gy, at least 60 Gy, at least 65 Gy, at least 68 Gy, at least 70 Gy, at least 72 Gy, and even at least 75 Gy. In certain embodiments, the overall dose does not exceed 80 Gy, such as not exceeding 78 Gy and even not exceeding 75 Gy. For example, the overall dose may be in a range of from 50 Gy to 75 Gy, such as from 55 Gy to 75 Gy, and even from 60 Gy to 70 Gy.

Other Cancer Therapies

[00154] In yet another embodiment, the pentaaza macrocyclic ring complex is administered with an anti-cancer agent comprising a chemotherapeutic agent. In chemotherapy, chemotherapeutic agents are administered to a patient to kill or control the growth of cancerous cells. A typical course of chemotherapy may include one or a plurality of doses of one or more chemotherapeutic agents, which can be administered over the course of days, weeks and even months. Chemotherapeutic agents can include at least one of: alkylating antineoplastic agents such as nitrogen mustards (e.g. cyclophosphamide, chlorambucil), nitrosoureas (e.g. n-nitroso-n-methylurea, carmustine, semustine), tetrazines (e.g. dacarbazine, mitozolimide), aziridines (e.g. thiotepa, mytomycin); anti-metabolites such as anti-folates (e.g. methotrexate and pemetrexed), fluoropyrimidines (e.g., fluorouracil, capecitabine), anthracyclines (e.g. doxorubicin, daunorubicin, epirubicin), deoxynucleoside analogs (e.g. cytarabine, gemcitabine, decitabine) and thiopurines (e.g., thioguanine, mercaptopurine); anti microtubule agents such as taxanes (e.g. paclitaxel, docetaxel); topoisomerase inhibitors (e.g. etoposide, doxorubicin, mitoxantrone, teniposide); and antitumor antibiotics (e.g. bleomycin, mitomycin). For example, the chemotherapeutic agent may be selected from the group consisting of all-trans retinoic acid, arsenic trioxide, azacitidine, azathioprine, bleomycin, carboplatin, capecitabine, cisplatin, chlorambucil, cyclophosphamide, cytarabine, daunorubicin, docetaxel, doxifluridine, doxorubicin, epirubicin, epothilone, etoposide, fluorouracil, gemcitabine, hydroxyurea, idarubicin, imatinib, mechlorethamine, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, pemetrexed, teniposide, tiguanine, valrubicin, vinblastine, vincristine, vindesine, and vinorelbine. The administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, N.J. 07645-1742, USA).

[00155] In one embodiment, the pentaaza macrocyclic ring complex is administered as a part of a course of therapy that includes an anti-cancer therapeutic agent comprising a chemotherapeutic agent selected from the group consisting of cisplatin, doxorubicin, bleomycin, and paclitaxel. Furthermore, in one embodiment, the additional chemotherapeutic agent may be selected from the group consisting of a taxane, an anticancer antibiotic, and an anthracycline. Other chemotherapeutic agents can include arsenic trioxide and 5-FU, which agents can also be used in the methods

and compositions described herein. (Alexandre *et al.*, Cancer Res. 67: (8), 3512-3517 (2007); Yen *et al.*, J. Clin. Invest. 98 (5), 1253-1260 (1996); Masuda *et al.*, Cancer Chemother. Pharmacol. 47(2), 155-160 (2001)).

5 [00156] According to yet another embodiment, the chemotherapeutic agent can include at least one of an antimetabolite anti-cancer agents and antimitotic anti-cancer agents, and combinations thereof, which may include some of the agents described above and well as other agents described further herein. Various antimetabolite and antimitotic agents may be employed in the methods and compositions described herein.

10 [00157] Antimetabolic agents typically structurally resemble natural metabolites, which are involved in normal metabolic processes of cancer cells such as the synthesis of nucleic acids and proteins. The antimetabolites, however, differ enough from the natural metabolites such that they interfere with the metabolic processes of cancer cells. In the cell, antimetabolites are mistaken for the metabolites they resemble, and are processed by the cell in a manner analogous to the normal
15 compounds. The presence of the "decoy" metabolites prevents the cells from carrying out vital functions and the cells are unable to grow and survive. For example, antimetabolites may exert cytotoxic activity by substituting these fraudulent nucleotides into cellular DNA, thereby disrupting cellular division, or by inhibition of critical cellular enzymes, which prevents replication of DNA.

20 [00158] In one embodiment, therefore, the antimetabolite agent is a nucleotide or a nucleotide analog. In certain embodiments, for example, the antimetabolite agent may comprise purine (e.g., guanine or adenosine) or analogs thereof, or pyrimidine (cytidine or thymidine) or analogs thereof, with or without an attached sugar moiety.

25 [00159] Suitable antimetabolite agents for use in the present disclosure may be generally classified according to the metabolic process they affect, and can include, but are not limited to, analogues and derivatives of folic acid, pyrimidines, purines, and cytidine. Thus, in one embodiment, the antimetabolite agent(s) is selected from the group consisting of cytidine analogs, folic acid analogs, purine analogs, pyrimidine analogs, and combinations thereof.

30 [00160] In one particular embodiment, for example, the antimetabolite agent is a cytidine analog. According to this embodiment, for example, the cytidine analog may

be selected from the group consisting of cytarabine (cytosine arabinoside), azacitidine (5-azacytidine), and salts, analogs, and derivatives thereof.

[00161] In another particular embodiment, for example, the antimetabolite agent is a folic acid analog. Folic acid analogs or antifolates generally function by inhibiting dihydrofolate reductase (DHFR), an enzyme involved in the formation of nucleotides; when this enzyme is blocked, nucleotides are not formed, disrupting DNA replication and cell division. According to certain embodiments, for example, the folic acid analog may be selected from the group consisting of denopterin, methotrexate (amethopterin), pemetrexed, pteropterin, raltitrexed, trimetrexate, and salts, analogs, and derivatives thereof.

[00162] In another particular embodiment, for example, the antimetabolite agent is a purine analog. Purine-based antimetabolite agents function by inhibiting DNA synthesis, for example, by interfering with the production of purine containing nucleotides, adenine and guanine which halts DNA synthesis and thereby cell division. Purine analogs can also be incorporated into the DNA molecule itself during DNA synthesis, which can interfere with cell division. According to certain embodiments, for example, the purine analog may be selected from the group consisting of acyclovir, allopurinol, 2-aminoadenosine, arabinosyl adenine (ara-A), azacitidine, azathioprine, 8-aza-adenosine, 8-fluoro-adenosine, 8-methoxy-adenosine, 8-oxo-adenosine, cladribine, deoxycoformycin, fludarabine, gancyclovir, 8-aza-guanosine, 8-fluoro-guanosine, 8-methoxy-guanosine, 8-oxo-guanosine, guanosine diphosphate, guanosine diphosphate-beta-L-2-aminofucose, guanosine diphosphate-D-arabinose, guanosine diphosphate-2-fluorofucose, guanosine diphosphate fucose, mercaptopurine (6-MP), pentostatin, thiamiprine, thioguanine (6-TG), and salts, analogs, and derivatives thereof.

[00163] In yet another particular embodiment, for example, the antimetabolite agent is a pyrimidine analog. Similar to the purine analogs discussed above, pyrimidine-based antimetabolite agents block the synthesis of pyrimidine-containing nucleotides (cytosine and thymine in DNA; cytosine and uracil in RNA). By acting as "decoys," the pyrimidine-based compounds can prevent the production of nucleotides, and/or can be incorporated into a growing DNA chain and lead to its termination. According to certain embodiments, for example, the pyrimidine analog may be selected from the group consisting of ancitabine, azacitidine, 6-azauridine, bromouracil (e.g., 5-

bromouracil), capecitabine, carmofur, chlorouracil (e.g. 5-chlorouracil), cytarabine (cytosine arabinoside), cytosine, dideoxyuridine, 3'-azido-3'-deoxythymidine, 3'-dideoxycytidin-2'-ene, 3'-deoxy-3'-deoxythymidin-2'-ene, dihydrouracil, doxifluridine, enocitabine, floxuridine, 5-fluorocytosine, 2-fluorodeoxycytidine, 3-fluoro-3'-deoxythymidine, fluorouracil (e.g., 5-fluorouracil (also known as 5-FU), gemcitabine, 5-methylcytosine, 5-propynylcytosine, 5-propynylthymine, 5-propynyluracil, thymine, uracil, uridine, and salts, analogs, and derivatives thereof. In one embodiment, the pyrimidine analog is other than 5-fluorouracil. In another embodiment, the pyrimidine analog is gemcitabine or a salt thereof.

10 [00164] In certain embodiments, the antimetabolite agent is selected from the group consisting of 5-fluorouracil, capecitabine, 6-mercaptopurine, methotrexate, gemcitabine, cytarabine, fludarabine, pemetrexed, and salts, analogs, derivatives, and combinations thereof. In other embodiments, the antimetabolite agent is selected from the group consisting of capecitabine, 6-mercaptopurine, methotrexate, gemcitabine, 15 cytarabine, fludarabine, pemetrexed, and salts, analogs, derivatives, and combinations thereof. In one particular embodiment, the antimetabolite agent is other than 5-fluorouracil. In a particularly preferred embodiment, the antimetabolite agent is gemcitabine or a salt or thereof (e.g., gemcitabine HCl (Gemzar®)).

[00165] Other antimetabolite agents may be selected from, but are not limited 20 to, the group consisting of acanthifolic acid, aminothiadiazole, brequinar sodium, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, Wellcome EHNA, Merck & Co. EX-015, fazarabine, fludarabine phosphate, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO- 25 152, 5-FU-fibrinogen, isopropyl pyrrolizine, Lilly LY-188011; Lilly LY-264618, methobenzaprim, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, tiazofurin, Erbamont TIF, tyrosine kinase inhibitors, Taiho UFT and uricytin, among others.

30 [00166] In one embodiment, the chemotherapeutic agent comprises an antimitotic agent that is a microtubule inhibitor or a microtubule stabilizer. In general, microtubule stabilizers, such as taxanes (some of which are also described above) and

epothilones, bind to the interior surface of the beta-microtubule chain and enhance microtubule assembly by promoting the nucleation and elongation phases of the polymerization reaction and by reducing the critical tubulin subunit concentration required for microtubules to assemble. Unlike microtubule inhibitors, such as the vinca
5 alkaloids, which prevent microtubule assembly, the microtubule stabilizers, such as taxanes, decrease the lag time and dramatically shift the dynamic equilibrium between tubulin dimers and microtubule polymers towards polymerization. In one embodiment, therefore, the microtubule stabilizer is a taxane or an epothilone. In another embodiment, the microtubule inhibitor is a vinca alkaloid.

10 [00167] One element of the therapy described herein may include the use of a taxane or derivative or analog thereof, some of which have also been discussed above. In one embodiment, the taxane may be a naturally derived compound or a related form, or may be a chemically synthesized compound or a derivative thereof, with antineoplastic properties. The taxanes are a family of terpenes, including, but not
15 limited to paclitaxel (Taxol®) and docetaxel (Taxotere®), which are derived primarily from the Pacific yew tree, *Taxus brevifolia*, and which have activity against certain tumors, particularly breast and ovarian tumors. In one embodiment, the taxane is docetaxel or paclitaxel. Paclitaxel is a preferred taxane and is considered an antimetabolic agent that promotes the assembly of microtubules from tubulin dimers and stabilizes
20 microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

[00168] Also included are a variety of known taxane derivatives, including both hydrophilic derivatives, and hydrophobic derivatives. Taxane derivatives include, but
25 are not limited to, galactose and mannose derivatives described in International Patent Application No. WO 99/18113; piperazino and other derivatives described in WO 99/14209; taxane derivatives described in WO 99/09021, WO 98/22451, and U.S. Patent No. 5,869,680; 6-thio derivatives described in WO 98/28288; sulfenamide derivatives described in U.S. Patent No. 5,821,263; deoxygenated paclitaxel
30 compounds such as those described in U.S. Patent No. 5,440,056; and taxol derivatives described in U.S. Patent No. 5,415,869. As noted above, it further includes prodrugs of paclitaxel including, but not limited to, those described in WO 98/58927; WO 98/13059; and U.S. Patent No. 5,824,701. The taxane may also be a taxane conjugate such as,

for example, paclitaxel-PEG, paclitaxel-dextran, paclitaxel-xylose, docetaxel-PEG, docetaxel-dextran, docetaxel-xylose, and the like. Other derivatives are mentioned in "Synthesis and Anticancer Activity of Taxol Derivatives," D. G. I. Kingston *et al.*, Studies in Organic Chemistry, vol. 26, entitled "New Trends in Natural Products Chemistry" (1986), Atta-ur-Rabman, P. W. le Quesne, Eds. (Elsevier, Amsterdam 1986), among other references. Each of these references is hereby incorporated by reference herein in its entirety.

[00169] Various taxanes may be readily prepared utilizing techniques known to those skilled in the art (see also WO 94/07882, WO 94/07881, WO 94/07880, WO 94/07876, WO 93/23555, WO 93/10076; U.S. Pat. Nos. 5,294,637; 5,283,253; 5,279,949; 5,274,137; 5,202,448; 5,200,534; 5,229,529; and EP 590,267) (each of which is hereby incorporated by reference herein in its entirety), or obtained from a variety of commercial sources, including for example, Sigma-Aldrich Co., St. Louis, MO.

[00170] Alternatively, the antimitotic agent can be a microtubule inhibitor; in one preferred embodiment, the microtubule inhibitor is a vinca alkaloid. In general, the vinca alkaloids are mitotic spindle poisons. The vinca alkaloid agents act during mitosis when chromosomes are split and begin to migrate along the tubules of the mitosis spindle towards one of its poles, prior to cell separation. Under the action of these spindle poisons, the spindle becomes disorganized by the dispersion of chromosomes during mitosis, affecting cellular reproduction. According to certain embodiments, for example, the vinca alkaloid is selected from the group consisting of vinblastine, vincristine, vindesine, vinorelbine, and salts, analogs, and derivatives thereof.

[00171] The antimitotic agent can also be an epothilone. In general, members of the epothilone class of compounds stabilize microtubule function according to mechanisms similar to those of the taxanes. Epothilones can also cause cell cycle arrest at the G2-M transition phase, leading to cytotoxicity and eventually apoptosis. Suitable epothilones include epothilone A, epothilone B, epothilone C, epothilone D, epothilone E, and epothilone F, and salts, analogs, and derivatives thereof. One particular epothilone analog is an epothilone B analog, ixabepilone (Ixempra™).

[00172] In certain embodiments, the antimitotic anti-cancer agent is selected from the group consisting of taxanes, epothilones, vinca alkaloids, and salts and combinations thereof. Thus, for example, in one embodiment the antimitotic agent is a

taxane. More preferably in this embodiment the antimitotic agent is paclitaxel or docetaxel, still more preferably paclitaxel. In another embodiment, the antimitotic agent is an epothilone (e.g., an epothilone B analog). In another embodiment, the antimitotic agent is a vinca alkaloid.

5 [00173] According to one embodiment, an anti-cancer therapeutic agent is provided that may be any one or more of a therapeutic agent that inhibits a hormone receptor pathway associated with growth or progression of the cancer (e.g. endocrine agents, which may be referred to as hormone therapy agents), and/or a chemotherapy agent. The endocrine agents are compounds that are capable of blocking or interfering with the effects of hormones on cancer cells (Lumachi et al., *Curr Med Chem*, 18(4)
10 513-522 (2011); Awan et al., *Curr Oncol*, 25(4): 285-291 (2018)). Cancer and/or tumor cells that contain hormone receptors and/or that depend on hormones for growth may be particularly responsive to endocrine therapy, such as for example estrogen receptor positive (ER positive) cells that use estrogen to grow. According to one embodiment,
15 the therapeutic agent that inhibits a hormone receptor pathway associated with growth or progression of the cancer targets any one or more of the estrogen receptor pathway, the progesterone receptor pathway, and the androgen receptor pathway. For example the therapeutic agent that targets any one or more of the estrogen receptor pathway, progesterone receptor pathway, and the androgen receptor pathway can comprises any
20 one or more of estrogen receptor inhibitors, estrogen receptor degraders/downregulators, selective estrogen receptor modulators (SERMs), aromatase inhibitors, GnRH agonists, androgen synthesis inhibitors, androgen receptor inhibitors, and selective progesterone receptor modulators (SPRMs). According to another embodiment, the endocrine therapy agent comprises a SERM compound
25 selected from the group consisting of tamoxifen, letrozole, clomifene, 4-hydroxytamoxifen, toremifene, raloxifene, nafoxidine, lasofoxifene, bazedoxifene, ospemifene, fulvestrant, brilanestrant, elacestrant, and derivatives, salts and/or prodrugs thereof. According to yet another embodiment, the endocrine therapy agent comprises a SERM compound having a triphenylethylene structure, and/or a
30 benzothiophene structure. According to yet a further embodiment, the endocrine therapy agent comprises a SERM that is any one selected from the group consisting of tamoxifen, 4-hydroxytamoxifen, and derivatives, prodrugs and/or salts thereof.

[00174] According to yet another embodiment, the anti-cancer therapeutic agent targets the androgen receptor pathway, and comprises any one or more of an androgen receptor antagonist, an androgen synthesis inhibitor and an antigonadotropin. For example, the therapeutic agent that targets the androgen receptor pathway can

5 comprise at least one selected from the group consisting of cyproterone acetate, megestrol acetate, chlormadinone acetate, spironolactone, oxendolone, osaterone acetate, flutamide, bicalutamide, nilutamide, topilutamide, enzalutamide, apalutamide, dienogest, drospirenone, medogestone, norgestimate acetate, norgestimate, trimegestone, ketoconazole, abiraterone acetate, seviteronel, aminoglutethimide,

10 finasteride, dutasteride, episteride, alfatradiol, cyproterone acetate, medrogestone, flutamide, nilutamide, bicalutamide, leuporelin, cetrorelix, allylestrenol, chlormadinone acetate, cyproterone acetate, gestonorone caproate, hydroxyprogesterone caproate, medroxyprogesterone acetate, megestrol acetate, osaterone acetate, oxendolone, estradiol, estradiol esters, ethinylestradiol, conjugated estrogens, diethylstilbestrol, and

15 derivatives, salts and/or prodrugs thereof.

[00175] According to yet another embodiment, the anti-cancer therapeutic agent targets the progesterone receptor pathway, and comprises any one or more comprises a Type I, Type II or Type III selective modulator of progesterone (SPRM) that is at least one selected from the group consisting onapristone, mifepristone, lonaprisan,

20 aglepristone, Org31710, Org31806, CDB-2914 and CDB-4124, and derivatives, salts and/or prodrugs thereof.

[00176] According to yet another embodiment, the anti-cancer therapeutic agent comprises a chemotherapeutic agent, such as any of a platinum-containing chemotherapeutic agent and an anthracycline chemotherapeutic agent. For example,

25 the chemotherapeutic agent can comprise any of a platinum-containing chemotherapeutic agent selected from the group consisting of cisplatin, oxaliplatin, carboplatin, nedaplatin, lobaplatin, heptaplatin, dicycloplatin, lipoplatin, LA-12, phosphaplatin, phenanthriplatin, prolindac, triplatin tetranitrate, picoplatin, satraplatin and/or pharmaceutically acceptable salts thereof, and/or an anthracycline

30 chemotherapeutic agent selected from the group consisting of doxorubicin, daunorubicin, epirubicin and idarubicin, and/or pharmaceutically acceptable salts thereof. Other chemotherapeutic agents described elsewhere herein may also be suitable.

[00177] According to yet another embodiment, the anti-cancer therapeutic agent comprises a cell cycle inhibitor such as a CDK4/6 inhibitor, such as any selected from the group consisting of group of palbociclib, abemaciclib, ribociclib, and derivatives, salts and/or prodrugs thereof.

5 [00178] In one embodiment, the pentaaza macrocyclic ring complex is administered within a predetermined time period before or after a dose of the anti-cancer therapeutic agent, or concomitantly with the anti-cancer therapeutic agent. For example, the pentaaza macrocyclic ring complex may be administered within 1 week, 48 hours, 24 hours, 12 hours, 6, hours, 2 hours, 1 hour or even within 30 minutes of the
10 patient receiving the dose of the anti-cancer therapeutic agent (either before or after the dose of chemotherapeutic agent). Other durations between the dose of the pentaaza macrocyclic ring complex and the anti-cancer therapeutic agent may also be suitable.

[00179] In one embodiment, a course of therapy with pentaaza macrocyclic ring complex, optionally with the anti-cancer therapeutic agent can comprise one or
15 multiple doses of the agent and/or complex, according to the treatment to be provided. In one embodiment, a course of therapy comprising one or multiple doses can comprise administering a dose of the pentaaza macrocyclic complex a predetermined period of time before administration of the anti-cancer therapeutic agent. For example, the course of therapy can comprise administering an initial dose and optionally one or more
20 subsequent doses of the anti-cancer therapeutic agent, with the onset of dosing with the pentaaza macrocyclic ring complex being performed a predetermined period of time before the initial anti-cancer therapeutic agent. In another embodiment, a course of therapy comprising one or multiple doses can comprise administering a dose of the pentaaza macrocyclic complex after a predetermined period of time has elapsed since
25 administration of a dose of anti-cancer therapeutic agent. That is, the course of therapy can comprise administering an initial dose and optionally one or more subsequent doses of the anti-cancer therapeutic agent, with the onset of dosing with the pentaaza macrocyclic ring complex being delayed for a predetermined period of time after the initial anti-cancer therapeutic agent.

30 [00180] In yet another embodiment, at least one of the pentaaza macrocyclic ring complex and/or the anti-cancer therapeutic agent is administered in combination

with both a radiation therapy and a chemotherapy involving administration of an additional chemotherapeutic agent.

Examples

[00181] The following non-limiting examples are provided to further illustrate aspects of the present invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent approaches the inventors have found function well in the practice of the invention, and thus can be considered to constitute examples of modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

[00182] Uncertainties in radiation-induced cancer risk estimation and its associated mortality rates are among the primary factors limiting the number of safe days an astronaut can spend in space. Initial cancer risks are based on epidemiological-based modeling and include cohorts such as the atomic bomb survivor life span study (LSS) whose estimates contain large confidence intervals. Furthermore, there is the need for adequate countermeasures to radiation effects for first responders to either nuclear accidents or terrorist incidents that broadly disperse radioactive materials, and, there is the need to identify countermeasures for both acute and late radiation sequelae (cancers) for large civilian populations exposed to such events.

[00183] The goal of the studies herein was to determine whether pentaazamacrocyclic dismutase mimetics, including the compound GC4419, would reduce the risk for lung and other cancers after particulate radiations that are representative of galactic cosmic rays (GCRsim) as well as for γ -ray exposures with doses comparable to what an astronaut may receive on a Mars mission, or what an individual might receive due to their proximity to a nuclear or terrorist event involving radionuclides or due to other radiation exposure, whether occupational, therapeutic or otherwise.

[00184] In addition, while reducing carcinogenesis might be expected to extend life span, radiation exposure has also been suggested to accelerate accumulations in other, non-malignant cellular damage. These include genetic and mitochondrial damage, as well as cell senescence, which might not manifest as acute disorders but

negatively impact life span. Therefore, survival of the animal model subjects was also determined.

[00185] GC4419 and other pentaaza macrocyclic selective dismutase mimetics (GC4403, GC4401, GC4711, etc.) have been shown to reduce overt acute and sub-chronic radiation damage such as mucositis, pulmonary pneumonitis and fibrosis and liver damage, as well as platinum therapy kidney damage. And they have been shown to enhance the efficacy of radiation and other therapies in treating established tumors. However, they have not been tested in the distinct biological setting of carcinogenesis.

[00186] **Materials & Methods:**

10 [00187] Animal Irradiation, Housing and Experimental Design:

[00188] All animal studies conducted used female BALB/c mice irradiated at 77-91 days of age and housed for a lifetime study to determine rates of carcinogenesis and survival. Animals were purchased from Charles River Laboratory, shipped to Brookhaven National Laboratory, and irradiated with the doses and ion species described below. Morbidity of mice was assessed daily and necropsy performed when animals became moribund or reach 750 days of age or where survival plots showed statistically significant differences in survival when comparing GC4419-treated animals vs. those that were not treated with GC4419 prior and after radiation. The number of mice per treatment cohort are given in Table 2.

20 [00189] GC4419 Treatment:

[00190] Animals were treated or not with GC4419. Those animals treated with GC4419 followed the following strategy. GC4419 was delivered at a dose of 24 mg/kg (mice were weighed prior to drug delivery) interperitoneally (i.p.) at roughly 45-60 minutes prior to radiation exposure. GC4419 was then provided i.p. for the next 6 days, and the animals were shipped to UT Southwestern (UTSW) Medical Center for temporary quarantine before returning to the animal facility. Upon return to UTSW the animals were treated with GC4419 i.p. weekly for another 11 weeks for a total of 12 weeks on treatment.

[00191] Radiation Treatment:

30 [00192] Radiation exposures were whole body. The galactic cosmic ray (GCR) simulation exposures used the beam line at the NASA Space Radiation Laboratory at

Brookhaven National Lab (BNL) and the γ -ray exposures used a ^{137}Cs source at BNL. Subsequent to single dose irradiation, animals were returned to their cages.

[00193] Galactic cosmic rays (GCR) are heavy ion radiation characteristic of the deep space environment, and the GCR simulation (GCRsim) at BNL mimics the
5 complex radiation environment in space. The GCRsim ions used are described in Table 1 below.

[00194] **Table 1.** Ion species used to irradiate animals in order of use, their nominal energy and the representative fraction of the total dose provided by each ion.

Ion	Energy (MeV/n)	LET (KeV/mm)	% of Total Dose
H	1000	0.22	35
Si	600	50.24	1
He	250	1.58	18
O	350	20.72	6
Fe	600	170.01	1
H	250	0.4	39

[00195] Results:

[00196] Figs. 1A-1D represent survival in cohorts where animals were exposed to single dose whole-body γ -rays or not irradiated (Control), and treated or not with GC4419. Figs. 1A-1B present preliminary results through approximately 400-600 days post-irradiation depending on the cohort. Figs. 1C-1D present final results. As expected, the survival curves show in the animals not treated with GC4419, trends to survival decreasing with increasing γ -ray dose from unirradiated Control to 0.75 Gy (Fig. 1B & 1D) to 1.5 Gy (Fig. 1A & 1C). Novelly, the final survival curves also show statistically significantly increased survival with GC4419 in both the 0.75 Gy (Fig. 1D; $p < 0.01$) and 1.5 Gy (Fig. 1 C; $p < 0.05$) γ -ray paired cohorts. In fact, survival in animals exposed to 0.75 Gy and treated with GC4419 had equivalent survival to unirradiated animals not treated with GC4419.

[00197] Figs. 2A-2D represent survival in cohorts where animals were exposed to single dose whole-body GCRsim radiation or not irradiated (Control), and treated or not with GC4419. Figs. 2A-2B present results, including preliminary data for unirradiated animals treated with GC4419 (Control + GC4419) cohort through approximately 400 days post-irradiation. Figs. 2C-2D present final results for all the presented cohorts. As with γ -rays, the survival curves show in the animals not treated with GC4419, trends to survival decreasing with increasing GCRsim dose from unirradiated control to 0.4 Gy to 0.75 Gy. The survival curves also show statistically significantly increased survival with GC4419 in the 0.75 Gy (* $p < 0.05$) GCRsim paired cohorts. In the 0.4 Gy GCRsim paired cohorts, treatment with GC4419 neither increases nor decreases survival. This may reflect that GCRsim is a combination of various radiations of varying carcinogenic potential curves.

[00198] Figs. 3A-3C represent survival in cohorts where unirradiated animals (Control) were treated or not with GC4419. Fig. 3A presents results through approximately 400 days post-irradiation with the range of the y-axis covering 95-100% survival. Fig. 3B-3C present final results with the ranges of the y-axis covering 0-100% and 70-100% survival. Unexpectedly, the survival curves show statistically significantly increased survival with GC4419, even in the unirradiated animals (** $p < 0.01$).

[00199] Pathological endpoints were also considered. Specifically, lung cancer induction, or carcinogenesis, and other tumors that are evident in numbers large enough to consider as secondary endpoints. These endpoints are described in the following tables and figure. The term "masses" is used to describe an abnormal growth, evident by eye, within a given tissue; for example, the term "lung masses" is used to describe abnormal tissues found in the lung that are collected for pathologic examination.

[00200] Given prior experience with the mouse model of radiation-induced carcinogenesis, it is expected that most, if not all, of the lung masses are tumors. For the ovarian masses, some proportion of the masses are expected to be tumors. For observations of hepatosplenomegaly, many of the enlarged livers and spleens may not reflect tumors of those organs. These may, however, may be present as result of hematologic malignancies, such as leukemias, but that was not assessed in this experiment.

[00201] Table 2 presents the incidence of lung masses observed at necropsy by treatment cohort, including preliminary data for certain γ -ray cohorts through approximately 600 days post-irradiation and for unirradiated animals treated with GC4419 (Control + GC4419) cohort through approximately 400 days post-irradiation. Fig. 4 presents final results for incidence of lung masses. In general, the incidence of lung masses in the final results was similar within the paired cohorts, however, there was markedly and statistically significantly decreased occurrence of lung masses with GC4419 in both the 0.75 Gy γ -ray ($p < 0.05$) and 0.75 Gy GCRsim ($p < 0.01$) paired cohorts. The absence of a clear difference in the final results of Fig. 4 in incidence of lung tumors within paired cohorts which show a clear improvement of survival with GC4419, such as 1.5 Gy γ -ray and unirradiated (Control) paired cohorts, suggests that GC4419 impact in increasing lifespan may involve other biological pathways besides carcinogenesis. However, since the incidence of tumors at necropsy measured across the range of animal ages at which each animal dies, the preliminary results in Table 2 suggest that this lack of a tight correlation between reduced carcinogenesis and increased survival may also reflect that as an animal lives longer it has a greater opportunity to develop cancer. In other words, in part GC4419 could have delayed carcinogenesis.

[00202] **Table 2.** Percentage mice with lung masses by treatment cohort.

Irradiation	GC4419	Dose (Gy)	# Mice	# Lung Masses	% Yield
GCRsim					
	-	0.75	248	52	21.0
	+	0.75	248	27	10.9
	-	0.4	359	36	10.0
	+	0.4	224	24	10.7
γ -ray					
	-	1.5	253	30	11.9
	+	1.5	248	16	6.5
	-	0.75	258	38	14.7
	+	0.75	248	15	6.0
None					
	-	0	395	42	10.6
	+	0	235	1	0.4

[00203] Table 3 presents the incidence of ovarian masses and hemorrhagic cysts observed at necropsy by treatment cohort, including preliminary data for certain γ -ray cohorts through approximately 600 days post-irradiation and for unirradiated animals treated with GC4419 (Control + GC4419) cohort through approximately 400 days post-irradiation. Fig. 4 presents final results for incidence of ovarian masses and hemorrhagic cysts. In general, the incidence of ovarian pathologies was similar or reduced in animals treated with GC4419 within the paired cohorts. There was markedly decreased occurrence of ovarian masses and hemorrhagic cysts with GC4419 in the unirradiated, 0.75 Gy GCRsim, and statistically significant 0.75 Gy γ -ray ($p < 0.05$) paired cohorts.

[00204] **Table 3.** Percentage of mice with ovarian masses or hemorrhagic cysts by treatment cohort.

Irradiation	GC4419	Dose (Gy)	# Mice	# Ovary Masses/ Cysts	% Yield
GCRsim					
	-	0.75	248	60	24.2
	+	0.75	248	43	17.3
	-	0.4	359	45	12.5
	+	0.4	224	26	11.6
γ -ray					
	-	1.5	253	56	21.7
	+	1.5	248	24	9.6
	-	0.75	258	64	28.9
	+	0.75	248	22	8.8
None					
	-	0	395	42	10.6
	+	0	235	0	0.0

[00205] Table 4 presents the incidence of hepatosplenomegaly observed at necropsy by treatment cohort, in general through approximately 700 days, for certain γ -ray cohorts through approximately 600 days post-irradiation, and for unirradiated animals treated with GC4419 (Control + GC4419) cohort through approximately 400 days post-irradiation. Consistent with the fact that for hepatosplenomegaly, many of the enlarged livers and spleens may not reflect tumors of those organs, unlike the case with lung masses or ovarian masses and hemorrhagic cysts, there is no consistent trend to increased or decreased incidence within paired cohorts.

[00206] **Table 4.** Percentage of mice with hepatosplenomegaly by treatment cohort.

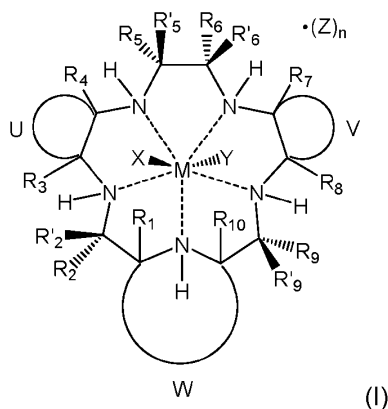
Irradiation	GC4419	Dose (Gy)	# Mice	# Enlarged	% Yield
GCRsim					
	-	0.75	248	19	7.7
	+	0.75	248	36	14.5
	-	0.4	359	50	13.9
	+	0.4	224	33	14.7
γ -ray					
	-	1.5	253	19	7.5
	+	1.5	248	17	6.8
	-	0.75	258	25	10.6
	+	0.75	248	9	3.6
None					
	-	0	395	20	5.1
	+	0	235	1	0.4

[00207] GC4419 appears to have an effect on survival in animals exposed to a variety of radiation types and doses, a response that is predominantly recapitulated when examining for other endpoints including the appearance of lung masses, which are presumed to reflect carcinogenesis, and hemorrhagic ovarian cysts and ovarian masses. As shown in Figs. 3A-3C, it also appears to increase survival in unirradiated animals, signaling an effect beyond improving survival and reducing tumor risk with radiation exposure. These suggest a role for pentaaza macrocyclic dismutase mimetics in reducing carcinogenesis and extending life span, even without the damaging effects of radiation.

[00208] The following Enumerated Embodiments are provided to illustrate aspects of the disclosure, although the embodiments are not intended to be limiting and other aspects and/or embodiments may also be provided.

[00209] Embodiment 1. A method of reducing the risk of carcinogenesis in a mammalian subject, the method comprising:

administering to the mammalian subject a therapeutically effective amount of a pentaaza macrocyclic ring complex corresponding to the Formula (I) below:



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 $-\text{OR}_{11}$, $-\text{NR}_{11}\text{R}_{12}$, $-\text{COR}_{11}$, $-\text{CO}_2\text{R}_{11}$, $-\text{CONR}_{11}\text{R}_{12}$, $-\text{SR}_{11}$, $-\text{SOR}_{11}$, $-\text{SO}_2\text{R}_{11}$, $-\text{SO}_2\text{NR}_{11}\text{R}_{12}$, $-\text{N}(\text{OR}_{11})(\text{R}_{12})$, $-\text{P}(\text{O})(\text{OR}_{11})(\text{OR}_{12})$, $-\text{P}(\text{O})(\text{OR}_{11})(\text{R}_{12})$, and $-\text{OP}(\text{O})(\text{OR}_{11})(\text{OR}_{12})$, 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.

[00210] Embodiment 2. The method according to Embodiment 1, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to a radiation exposure.

[00211] Embodiment 3. The method according to any preceding Embodiment, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis due to a therapeutic radiation exposure.

[00212] Embodiment 4. The method according to any preceding Embodiment, wherein the mammalian subject has been exposed to radiation as a part of a course of radiation therapy provided to treat cancer.

[00213] Embodiment 5. The method according to any preceding Embodiment, wherein the mammalian subject will be exposed to radiation as a part of a course of radiation therapy provided to treat cancer.

[00214] Embodiment 6. The method according to any preceding Embodiment, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis due to a non-therapeutic radiation exposure

[00215] Embodiment 7. The method according to any preceding Embodiment, wherein the mammalian subject has been exposed to radiation during travel beyond the upper atmosphere of the Earth.

[00216] Embodiment 8. The method according to any preceding Embodiment, wherein the mammalian subject will be exposed to radiation during travel beyond the upper atmosphere of the Earth.

[00217] Embodiment 9. The method according to any preceding Embodiment, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to exposure to gamma radiation.

[00218] Embodiment 10. The method according to any preceding Embodiment, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to exposure to cosmic ray radiation.

[00219] Embodiment 11. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered before, during or after a dose of radiation provided during a course of therapy provided to treat cancer.

[00220] Embodiment 12. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered up to 1 min, 5 mins, 15 mins, 30 mins, 1 hour, 6 hours, 12 hours, 1 day, 3 days, 5 days, 1 week, 2 weeks, 1 month, 3 months and/or 6 months before a dose of radiation provided during a course of therapy provided to treat cancer.

[00221] Embodiment 13. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered at least one hour, at least one day, at least 3 days, at least 5 days, at least a week, at least 2 weeks, at least a month, at least 3 months, at least 6 months, at least a year, or at least 2 years, after a dose of radiation provided during a course of radiation therapy to treat cancer.

[00222] Embodiment 14. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered both before and after a dose of radiation provided during a course of radiation therapy to treat cancer.

[00223] Embodiment 15. The method according to any preceding Embodiment, wherein multiple doses of the pentaaza macrocyclic ring complex are administered after a dose of radiation provided during a course of radiation therapy to treat cancer.

[00224] Embodiment 16. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered before,

during or after an exposure to cosmic ray or gamma ray radiation occurring as a part of travel beyond the upper atmosphere of the Earth.

[00225] Embodiment 17. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered up to 1 min, 5 mins, 15 mins, 30 mins, 1 hour, 6 hours, 12 hours, 1 day, 3 days, 5 days, 1 week, 2 weeks, 1 month, 3 months and/or 6 months before an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

[00226] Embodiment 18. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered at least one hour, at least one day, at least 3 days, at least 5 days, at least a week, at least 2 weeks, at least a month, at least 3 months, at least 6 months, at least a year, or at least 2 years, after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

[00227] Embodiment 19. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered both before and after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

[00228] Embodiment 20. The method according to any preceding Embodiment, wherein multiple doses of the pentaaza macrocyclic ring complex are administered after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

[00229] Embodiment 21. The method according to any preceding Embodiment, wherein the mammalian subject is afflicted with cancer.

[00230] Embodiment 22. The method according to any preceding Embodiment, wherein the mammalian subject is in remission from cancer.

[00231] Embodiment 23. The method of any preceding Embodiment, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of lung tumors.

[00232] Embodiment 24. The method of any preceding Embodiment, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of liver tumors.

[00233] Embodiment 25. The method of any preceding Embodiment, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of tumors of the spleen.

[00234] Embodiment 26. The method of any preceding Embodiment, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of ovarian tumors.

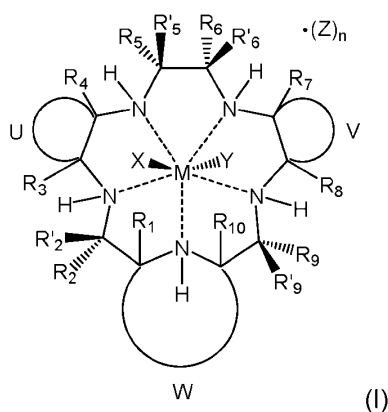
[00235] Embodiment 27. The method of any preceding Embodiment, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of any one or more of leukemia, lymphoma, breast, bladder, colon, liver, lung, esophagus, ovarian, multiple myeloma, spleen, and stomach cancers.

[00236] Embodiment 28. The method of any preceding Embodiment, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of any of leukemia and lymphoma.

[00237] Embodiment 29. The method of any preceding Embodiment, wherein the mammalian subject is a human subject.

[00238] Embodiment 30. A method of increasing the lifespan of a mammalian subject, the method comprising:

administering to the mammalian subject a therapeutically effective amount of a pentaaza macrocyclic ring complex corresponding to the Formula (I) below:



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.

[00239] Embodiment 31. The method according to Embodiment 30, comprising administering the pentaaza macrocyclic ring complex to the mammalian

subject for at least 1 month, at least 3 months, at least 6 months, at least 1 year, at least 3 years, at least 5 years and/or at least 1 decade.

[00240] Embodiment 32. The method according to any of Embodiments 30-31, comprising administering the pentaaza macrocyclic ring complex to the mammalian subject for no more than 2 decades, no more than 1 decade, no more than 5 yrs, no more than 3 years, no more than 1 year, no more than 6 months, no more than 3 months, and/or no more than 1 month.

[00241] Embodiment 33. The method according to any of Embodiments 30-32, comprising administering the pentaaza macrocyclic ring complex to the mammalian subject twice per day, once per day, every other day, weekly, bi-weekly, monthly, and/or bi-monthly.

[00242] Embodiment 34. The method according to any of Embodiments 30-33, comprising administering the pentaaza macrocyclic ring complex to the mammalian subject only in first decade of life, in the second decade of life, in the third decade of life, in the fourth decade of life, in the fifth decade of life, in the sixth decade of life, in the seventh decade of life and/or in the eighth decade of life, or in a combination thereof.

[00243] Embodiment 35. The method according to any of Embodiments 30-4, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to a radiation exposure

[00244] Embodiment 36. The method according to any of Embodiments 30-35, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis due to a therapeutic radiation exposure.

[00245] Embodiment 37. The method according to any of Embodiments 30-36, wherein the mammalian subject has been exposed to radiation as a part of a course of radiation therapy provided to treat cancer.

[00246] Embodiment 38. The method according to any of Embodiments 30-37, wherein the mammalian subject will be exposed to radiation as a part of a course of radiation therapy provided to treat cancer.

[00247] Embodiment 39. The method according to any of Embodiments 30-38, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis due to a non-therapeutic radiation exposure.

[00248] Embodiment 40. The method according to any of Embodiments 30-35, wherein the mammalian subject has been exposed to radiation during travel beyond the upper atmosphere of the Earth.

[00249] Embodiment 41. The method according to any of Embodiments 30-40, wherein the mammalian subject will be exposed to radiation during travel beyond the upper atmosphere of the Earth.

[00250] Embodiment 42. The method according to any of Embodiments 30-41, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to exposure to gamma radiation.

[00251] Embodiment 4. The method according to any of Embodiments 30-42, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to exposure to cosmic ray radiation.

[00252] Embodiment 44. The method according to any of Embodiments 30-43, wherein the pentaaza macrocyclic ring complex is administered before, during or after a dose of radiation provided during a course of therapy provided to treat cancer.

[00253] Embodiment 45. The method according to any of Embodiments 30-44, wherein the pentaaza macrocyclic ring complex is administered up to 1 min, 5 mins, 15 mins, 30 mins, 1 hour, 6 hours, 12 hours, 1 day, 3 days, 5 days, 1 week, 2 weeks, 1 month, 3 months and/or 6 months before a dose of radiation provided during a course of therapy provided to treat cancer.

[00254] Embodiment 46. The method according to any of Embodiments 30-45, wherein the pentaaza macrocyclic ring complex is administered at least one hour, at least one day, at least 3 days, at least 5 days, at least a week, at least 2 weeks, at least a month, at least 3 months, at least 6 months, at least a year, or at least 2 years, after a dose of radiation provided during a course of radiation therapy to treat cancer.

[00255] Embodiment 47. The method according to any of Embodiments 30-46, wherein the pentaaza macrocyclic ring complex is administered both before and after a dose of radiation provided during a course of radiation therapy to treat cancer.

[00256] Embodiment 48. The method according to any of Embodiments 30-47, wherein multiple doses of the pentaaza macrocyclic ring complex are administered after a dose of radiation provided during a course of radiation therapy to treat cancer.

[00257] Embodiment 49. The method according to any of Embodiments 30-48, wherein the pentaaza macrocyclic ring complex is administered before, during or after an exposure to cosmic ray or gamma ray radiation occurring as a part of travel beyond the upper atmosphere of the Earth.

[00258] Embodiment 50. The method according to any of Embodiments 30-49, wherein the pentaaza macrocyclic ring complex is administered up to 1 min, 5 mins, 15 mins, 30 mins, 1 hour, 6 hours, 12 hours, 1 day, 3 days, 5 days, 1 week, 2 weeks, 1 month, 3 months and/or 6 months before an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

[00259] Embodiment 51. The method according to any of Embodiments 30-50, wherein the pentaaza macrocyclic ring complex is administered at least one hour, at least one day, at least 3 days, at least 5 days, at least a week, at least 2 weeks, at least a month, at least 3 months, at least 6 months, at least a year, or at least 2 years, after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

[00260] Embodiment 52. The method according to any of Embodiments 30-51, wherein the pentaaza macrocyclic ring complex is administered both before and after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth

[00261] Embodiment 53. The method according to any of Embodiments 30-52, wherein multiple doses of the pentaaza macrocyclic ring complex are administered after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

[00262] Embodiment 54. The method according to any of Embodiments 30-53, wherein the mammalian subject is afflicted with cancer.

[00263] Embodiment 55. The method according to any of Embodiments 30-54, wherein the mammalian subject is in remission from cancer.

[00264] Embodiment 56. The method of any of Embodiments 30-55, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of lung tumors.

[00265] Embodiment 57. The method of any of Embodiments 30-56, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of liver tumors.

[00266] Embodiment 58. The method of any of Embodiments 30-57, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of ovarian tumors.

[00267] Embodiment 59. The method of any of Embodiments 30-58, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of any one or more of leukemia, lymphoma, breast, bladder, colon, liver, lung, esophagus, ovarian, multiple myeloma, and stomach cancers.

[00268] Embodiment 60. The method of any of Embodiments 30-59, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of any of leukemia and lymphoma.

[00269] Embodiment 61. The method of any of Embodiments 30-60, wherein the mammalian subject is a human subject.

[00270] Embodiment 62. The method of Embodiment 30, wherein the mammalian subject has not been and will not be subject to therapeutic radiation.

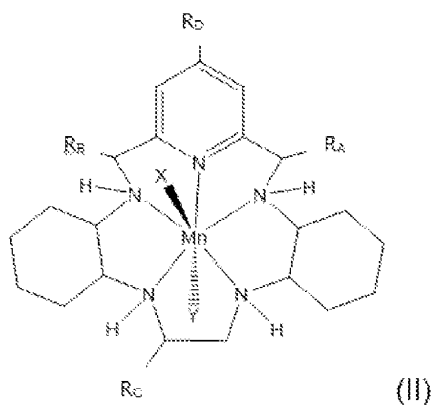
[00271] Embodiment 63. The method of any of Embodiments 30 and 62 wherein the mammalian subject is not at increased risk of carcinogenesis due to therapeutic or non-therapeutic radiation exposure.

[00272] Embodiment 64. The method according to any preceding Embodiment, 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.

[00273] Embodiment 65. The method according to any preceding Embodiment, wherein W is an unsubstituted pyridine moiety.

[00274] Embodiment 66. The method according to any preceding Embodiment, wherein U and V are transcyclohexanyl fused rings.

[00275] Embodiment 67. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is represented by Formula (II)

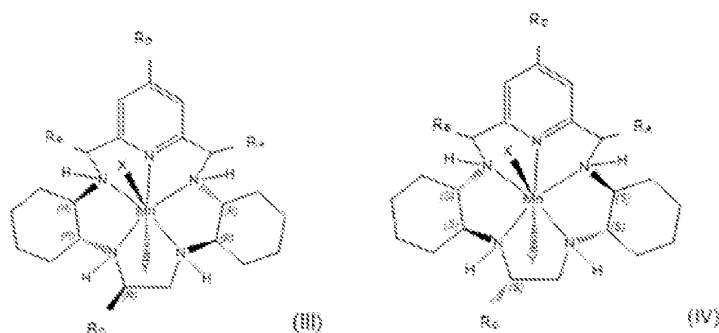


wherein

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

[00276] Embodiment 68. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is represented by Formula (III) or Formula (IV):



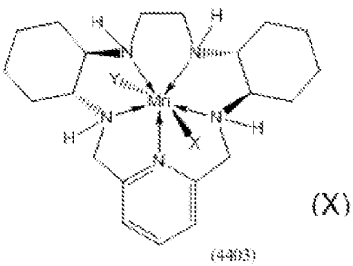
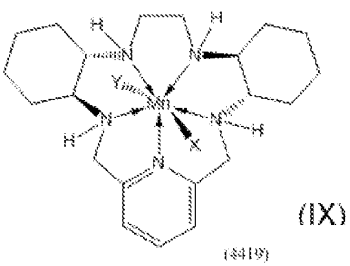
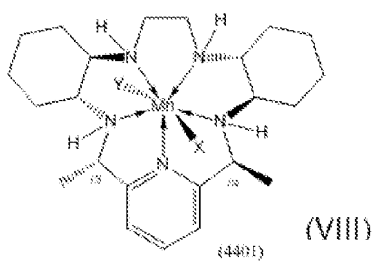
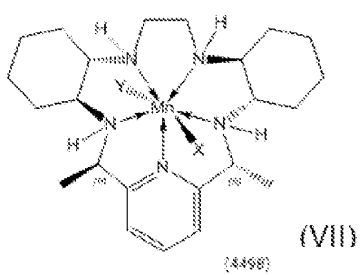
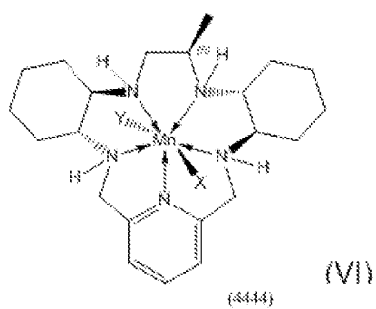
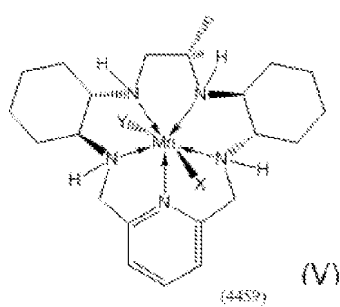
wherein

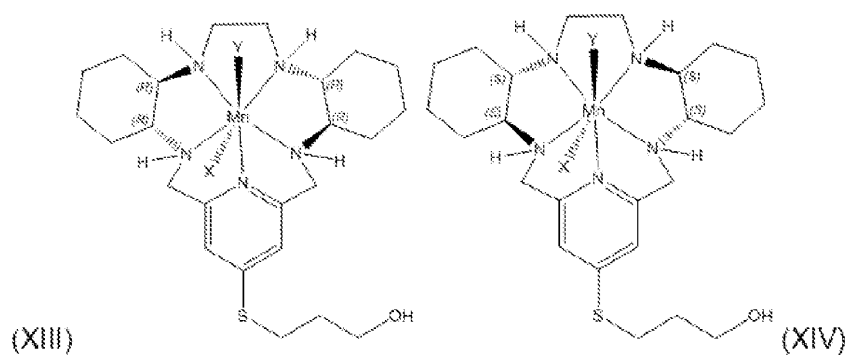
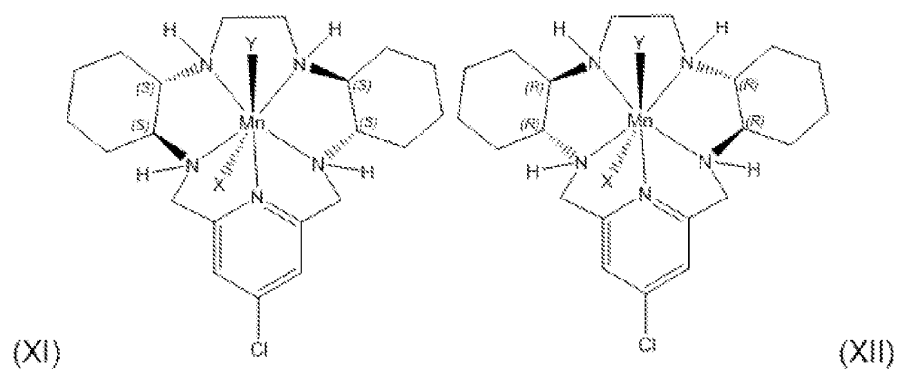
X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and

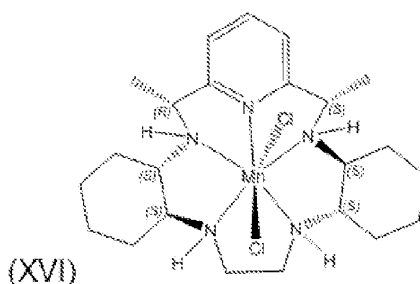
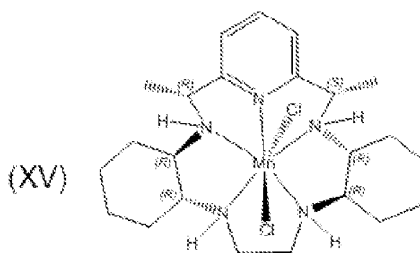
R_A , R_B , R_C , and R_D are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting

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

[00277] Embodiment 69. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is a compound represented by a formula selected from the group consisting of Formulae (V)-(XVI):







[00278] Embodiment 70. The method according to any preceding Embodiment, 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

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;

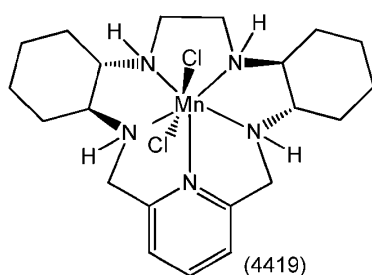
or X and Y are independently attached to one or more of R_1 , R_2 , R'_2 , R_3 , R_4 , R_5 , R'_5 , R_6 , R'_6 , R_7 , R_8 , R_9 , R'_9 , and R_{10} .

[00279] Embodiment 71. The method according to any preceding Embodiment, wherein X and Y are independently selected from the group consisting of fluoro, chloro, bromo, and iodo anions.

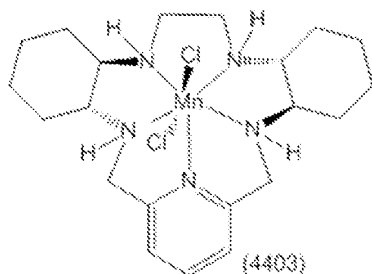
[00280] Embodiment 72. The method according to any preceding Embodiment, wherein X and Y are independently selected from the group consisting of alkyl carboxylates, aryl carboxylates and arylalkyl carboxylates.

[00281] Embodiment 73. The method according to any preceding Embodiment, wherein X and Y are independently amino acids.

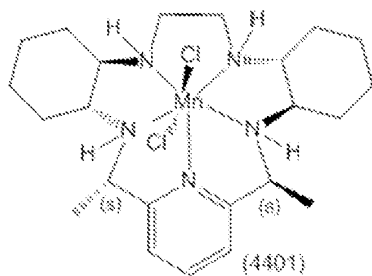
[00282] Embodiment 74. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



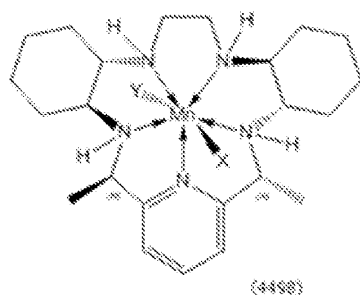
[00283] Embodiment 75. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



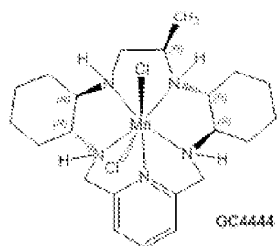
[00284] Embodiment 76. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



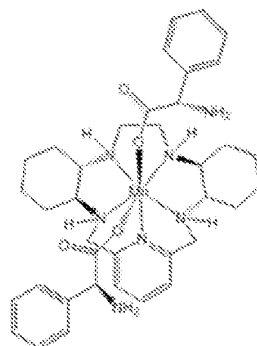
[00285] Embodiment 77. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is represented by the formula:



[00286] Embodiment 78. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is represented by the formula:

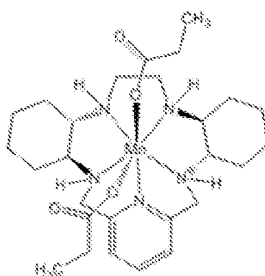


[00287] Embodiment 79. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is represented by the formula:



GC4702

[00288] Embodiment 80. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is represented by the formula:



GC4711

[00289] Embodiment 81. The method according to any preceding Embodiment, 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.

[00290] Embodiment 82. The method according to any preceding Embodiment, 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.

[00291] Embodiment 83. The method according to any preceding Embodiment, 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.

[00292] Embodiment 84. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered via at least one of parenteral route and oral route.

[00293] Embodiment 85. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered intraperitoneally or intravenously.

[00294] Embodiment 86. A kit for reducing carcinogenesis and/or increasing the lifespan of a mammalian subject, the kit comprising:

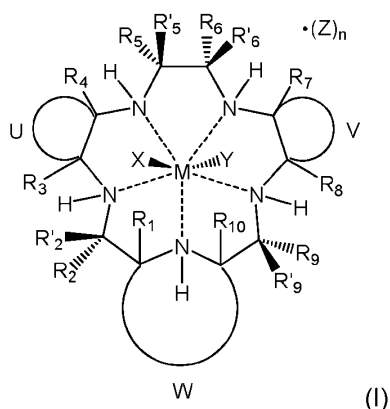
the pentaaza macrocyclic ring complex corresponding to Formula (I); and

instructions for administering a therapeutically effective amount of the pentaaza macrocyclic ring complex in accordance with a method according to any of the preceding Embodiments.

WHAT IS CLAIMED IS:

1. A method of reducing the risk of carcinogenesis in a mammalian subject, the method comprising:

administering to the mammalian subject a therapeutically effective amount of a pentaaza macrocyclic ring complex corresponding to the Formula (I) below:



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 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.

2. The method according to claim 1, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to a radiation exposure.
- 5 3. The method according to any preceding claim, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis due to a therapeutic radiation exposure.
- 10 4. The method according to any preceding claim, wherein the mammalian subject has been exposed to radiation as a part of a course of radiation therapy provided to treat cancer.

5. The method according to any preceding claim, wherein the mammalian subject will be exposed to radiation as a part of a course of radiation therapy provided to treat cancer.
- 5 6. The method according to any preceding claim, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis due to a non-therapeutic radiation exposure
- 10 7. The method according to any preceding claim, wherein the mammalian subject has been exposed to radiation during travel beyond the upper atmosphere of the Earth.
- 15 8. The method according to any preceding claim, wherein the mammalian subject will be exposed to radiation during travel beyond the upper atmosphere of the Earth.
- 20 9. The method according to any preceding claim, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to exposure to gamma radiation.
- 25 10. The method according to any preceding claim, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to exposure to cosmic ray radiation.
- 30 11. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered before, during or after a dose of radiation provided during a course of therapy provided to treat cancer.
- 30 12. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered up to 1 min, 5 mins, 15 mins, 30 mins, 1 hour, 6 hours, 12 hours, 1 day, 3 days, 5 days, 1 week, 2 weeks, 1 month, 3

months and/or 6 months before a dose of radiation provided during a course of therapy provided to treat cancer.

- 5 13. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered at least one hour, at least one day, at least 3 days, at least 5 days, at least a week, at least 2 weeks, at least a month, at least 3 months, at least 6 months, at least a year, or at least 2 years, after a dose of radiation provided during a course of radiation therapy to treat cancer.
- 10 14. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered both before and after a dose of radiation provided during a course of radiation therapy to treat cancer.
- 15 15. The method according to any preceding claim, wherein multiple doses of the pentaaza macrocyclic ring complex are administered after a dose of radiation provided during a course of radiation therapy to treat cancer.
- 20 16. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered before, during or after an exposure to cosmic ray or gamma ray radiation occurring as a part of travel beyond the upper atmosphere of the Earth.
- 25 17. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered up to 1 min, 5 mins, 15 mins, 30 mins, 1 hour, 6 hours, 12 hours, 1 day, 3 days, 5 days, 1 week, 2 weeks, 1 month, 3 months and/or 6 months before an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.
- 30 18. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered at least one hour, at least one day, at least 3 days, at least 5 days, at least a week, at least 2 weeks, at least a month, at least 3

months, at least 6 months, at least a year, or at least 2 years, after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

5 19. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered both before and after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

10 20. The method according to any preceding claim, wherein multiple doses of the pentaaza macrocyclic ring complex are administered after an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

15 21. The method according to any preceding claim, wherein the mammalian subject is afflicted with cancer.

22. The method according to any preceding claim, wherein the mammalian subject is in remission from cancer.

20 23. The method of any preceding claim, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of lung tumors.

24. The method of any preceding claim, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of liver tumors.

25 25. The method of any preceding claim, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of tumors of the spleen.

30 26. The method of any preceding claim, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of ovarian tumors.

27. The method of any preceding claim, wherein the administration of the pentaaza
 macrocyclic ring complex reduces the risk of any one or more of leukemia,
 lymphoma, breast, bladder, colon, liver, lung, esophagus, ovarian, multiple
 5 myeloma, spleen, and stomach cancers.

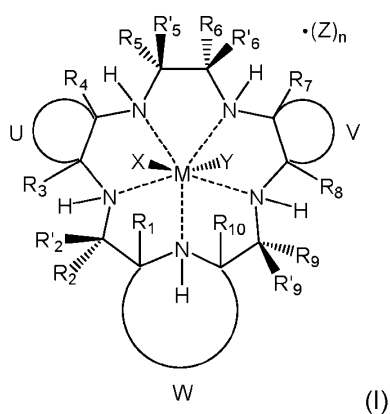
28. The method of any preceding claim, wherein the administration of the pentaaza
 macrocyclic ring complex reduces the risk of any of leukemia and lymphoma

10

29. The method of any preceding claim, wherein the mammalian subject is a human
 subject.

30. A method of increasing the lifespan of a mammalian subject, the method
 15 comprising:

administering to the mammalian subject a therapeutically effective amount of a
 pentaaza macrocyclic ring complex corresponding to the Formula (I) below:



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.

- 5 31. The method according to claim 30, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to a radiation exposure.

32. The method according to any of claims 30-31, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis due to a therapeutic radiation exposure.

5

33. The method according to any of claims 30-32, wherein the mammalian subject has been exposed to radiation as a part of a course of radiation therapy provided to treat cancer.

10

34. The method according to any of claims 30-33, wherein the mammalian subject will be exposed to radiation as a part of a course of radiation therapy provided to treat cancer.

15

35. The method according to any of claims 30-34, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis due to a non-therapeutic radiation exposure

20

36. The method according to any of claims 30-35, wherein the mammalian subject has been exposed to radiation during travel beyond the upper atmosphere of the Earth.

25

37. The method according to any of claims 30-36, wherein the mammalian subject will be exposed to radiation during travel beyond the upper atmosphere of the Earth.

30

38. The method according to any of claims 30-37, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to exposure to gamma radiation.

39. The method according to any of claims 30-38, wherein the mammalian subject is at increased risk of carcinogenesis, or will be at increased risk of carcinogenesis, due to exposure to cosmic ray radiation.

40. The method according to any of claims 30-39, wherein the pentaaza macrocyclic ring complex is administered before, during or after a dose of radiation provided during a course of therapy provided to treat cancer.
- 5
41. The method according to any of claims 30-40, wherein the pentaaza macrocyclic ring complex is administered up to 1 min, 5 mins, 15 mins, 30 mins, 1 hour, 6 hours, 12 hours, 1 day, 3 days, 5 days, 1 week, 2 weeks, 1 month, 3 months and/or 6 months before a dose of radiation provided during a course of therapy provided to treat cancer.
- 10
42. The method according to any of claims 30-41, wherein the pentaaza macrocyclic ring complex is administered at least one hour, at least one day, at least 3 days, at least 5 days, at least a week, at least 2 weeks, at least a month, at least 3 months, at least 6 months, at least a year, or at least 2 years, after a dose of radiation provided during a course of radiation therapy to treat cancer.
- 15
43. The method according to any of claims 30-42, wherein the pentaaza macrocyclic ring complex is administered both before and after a dose of radiation provided during a course of radiation therapy to treat cancer.
- 20
44. The method according to any of claims 30-43, wherein multiple doses of the pentaaza macrocyclic ring complex are administered after a dose of radiation provided during a course of radiation therapy to treat cancer.
- 25
45. The method according to any of claims 30-44, wherein the pentaaza macrocyclic ring complex is administered before, during or after an exposure to cosmic ray or gamma ray radiation occurring as a part of travel beyond the upper atmosphere of the Earth.
- 30
46. The method according to any of claims 30-45, wherein the pentaaza macrocyclic ring complex is administered up to 1 min, 5 mins, 15 mins, 30 mins,

1 hour, 6 hours, 12 hours, 1 day, 3 days, 5 days, 1 week, 2 weeks, 1 month, 3 months and/or 6 months before an exposure to cosmic ray or gamma ray radiation as a part of travel beyond the upper atmosphere of the Earth.

5 47. The method according to any of claims 30-46, wherein the pentaaza macrocyclic
ring complex is administered at least one hour, at least one day, at least 3 days,
at least 5 days, at least a week, at least 2 weeks, at least a month, at least 3
months, at least 6 months, at least a year, or at least 2 years, after an exposure
to cosmic ray or gamma ray radiation as a part of travel beyond the upper
10 atmosphere of the Earth.

48. The method according to any of claims 30-47, wherein the pentaaza macrocyclic
ring complex is administered both before and after an exposure to cosmic ray or
gamma ray radiation as a part of travel beyond the upper atmosphere of the
Earth.

15 49. The method according to any of claims 30-48, wherein multiple doses of the
pentaaza macrocyclic ring complex are administered after an exposure to cosmic
ray or gamma ray radiation as a part of travel beyond the upper atmosphere of
the Earth.

20 50. The method according to any of claims 30-49, wherein the mammalian subject is
afflicted with cancer.

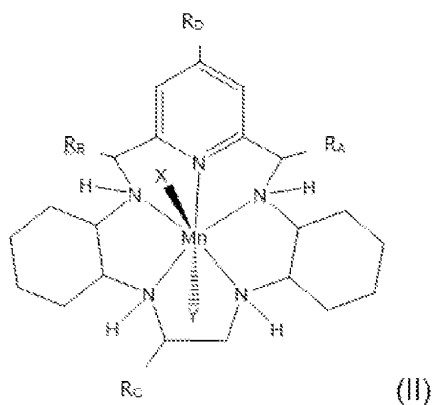
25 51. The method according to any of claims 30-50, wherein the mammalian subject is
in remission from cancer.

52. The method of any of claims 30-51, wherein the administration of the pentaaza
macrocyclic ring complex reduces the risk of lung tumors.

53. The method of any of claims 30-52, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of liver tumors.
54. The method of any of claims 30-53, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of ovarian tumors.
55. The method of any of claims 30-54, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of any one or more of leukemia, lymphoma, breast, bladder, colon, liver, lung, esophagus, ovarian, multiple myeloma, and stomach cancers.
56. The method of any of claims 30-55, wherein the administration of the pentaaza macrocyclic ring complex reduces the risk of any of leukemia and lymphoma
57. The method of any of claims 30-56, wherein the mammalian subject is a human subject.
58. The method of claim 30, wherein the mammalian subject has not been and will not be subject to therapeutic radiation.
59. The method of any of claims 30 and 58 wherein the mammalian subject is not at increased risk of carcinogenesis due to therapeutic or non-therapeutic radiation exposure.
60. The method according to any preceding claim, wherein R₁, R₂, R'₂, R₃, R₄, R₅, R'₅, R₆, R'₆, R₇, R₈, R₉, R'₉, and R₁₀ are each hydrogen.
61. The method according to any preceding claim, wherein W is an unsubstituted pyridine moiety.
62. The method according to any preceding claim, wherein U and V are

transcyclohexanyl fused rings.

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



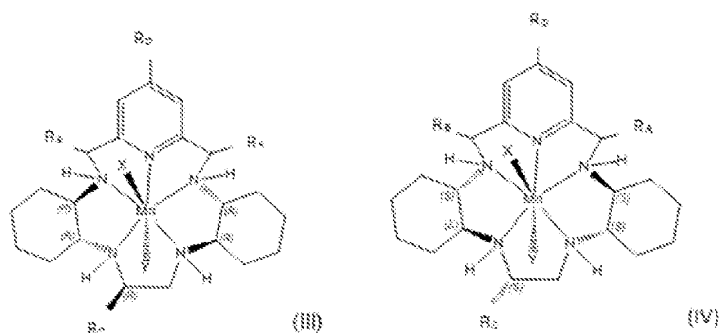
wherein

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.

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



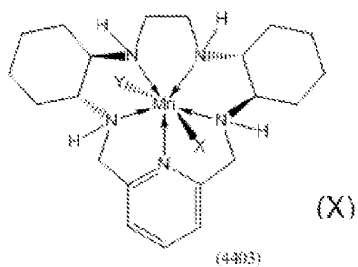
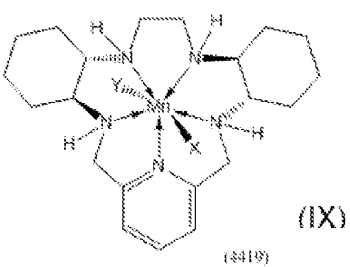
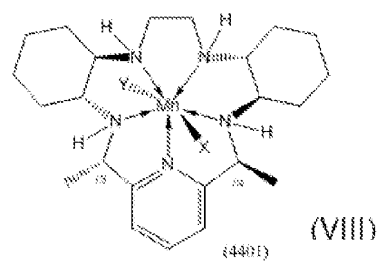
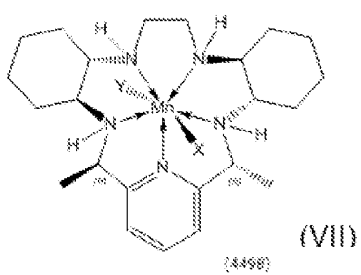
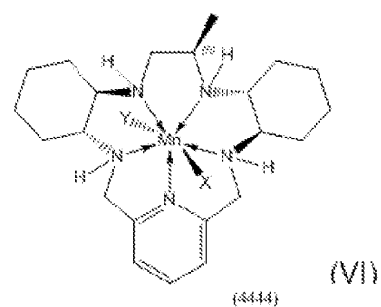
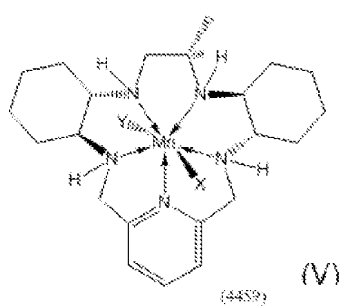
wherein

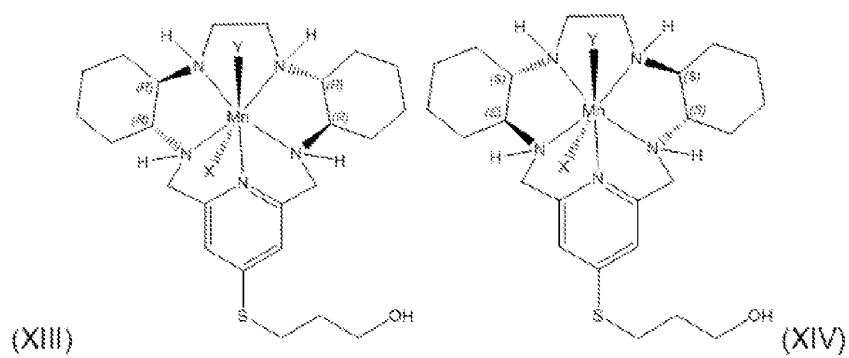
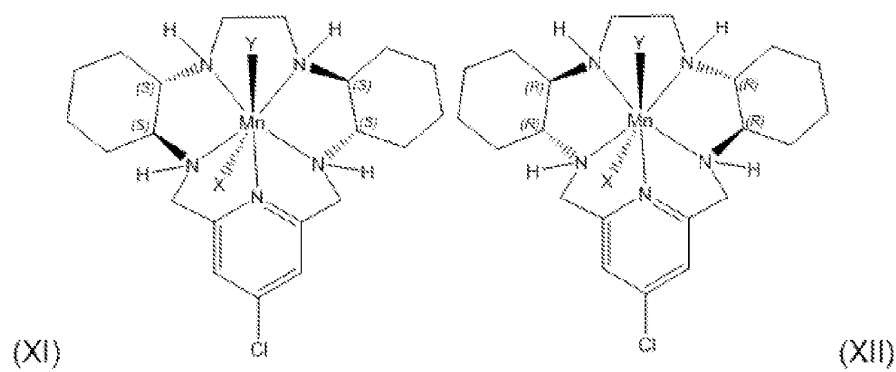
X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and

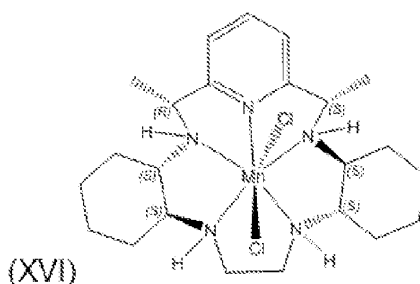
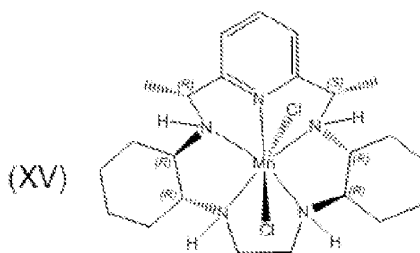
R_A , R_B , R_C , and R_D are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting

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

65. 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):







66. 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, peroxo, hydroperoxo, alkylperoxo, arylperoxo, 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

5 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

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;

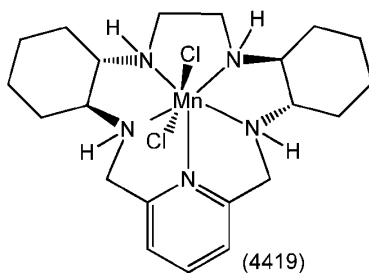
or X and Y are independently attached to one or more of R_1 , R_2 , R'_2 , R_3 , R_4 , R_5 , R'_5 , R_6 , R'_6 , R_7 , R_8 , R_9 , R'_9 , and R_{10} .

10 67. 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.

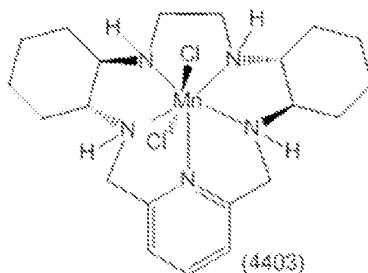
68. The method according to any preceding claim, wherein X and Y are independently selected from the group consisting of alkyl carboxylates, aryl carboxylates and arylalkyl carboxylates.

5 69. The method according to any preceding claim, wherein X and Y are independently amino acids.

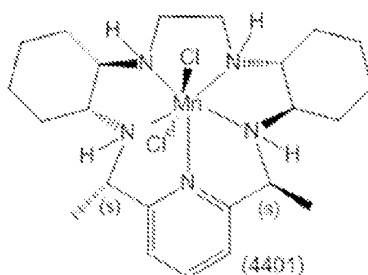
70. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



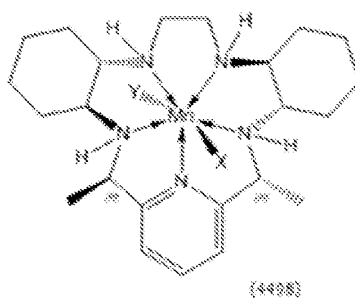
71. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



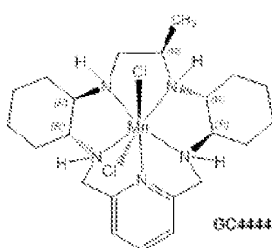
72. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



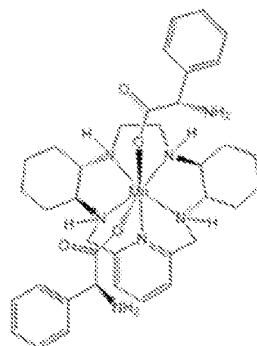
5 73. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is represented by the formula:



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

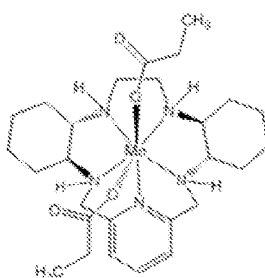


75. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is represented by the formula:



GC4702

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



GC4711

77. 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.
- 5 78. 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 24 mg/kg.
79. 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 10 mg/kg.
- 10 80. 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.
- 15 81. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered intraperitoneally or intravenously.
82. A kit for reducing carcinogenesis and/or increasing the lifespan of a mammalian subject, the kit comprising:
- the pentaaza macrocyclic ring complex corresponding to Formula (I); and
- instructions for administering a therapeutically effective amount of the pentaaza macrocyclic ring complex in accordance with a method according to any of the preceding claims.