Claims

What is claimed is:

1. A method for the formation of a tissue-targeting thorium complex, said method comprising:
    a) forming an octadentate chelator comprising four hydroxypyridinone (HOPO) moieties, substituted in the N-position with a C_1-C_3 alkyl group, and a coupling moiety terminating in a carboxylic acid group;
    b) coupling said octadentate chelator to at least one tissue-targeting peptide or protein comprising at least one amine moiety by means of at least one amide-coupling reagent whereby to generate a tissue-targeting chelator; and
    c) contacting said tissue-targeting chelator with an aqueous solution comprising an ion of at least one alpha-emitting thorium isotope.

2. The method of claim 1 wherein step b) is conducted in aqueous solution.

3. The method of claim 1 or claim 2 wherein said amide-coupling reagent is functional in aqueous solution.

4. The method of any preceding claim wherein said amide-coupling reagent is a carbodiimide coupling reagent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimid (EDC), N,N'-diisopropylcarbodiimid (DIC) or N,N'-dicyclohexylcarbodiimid (DCC).

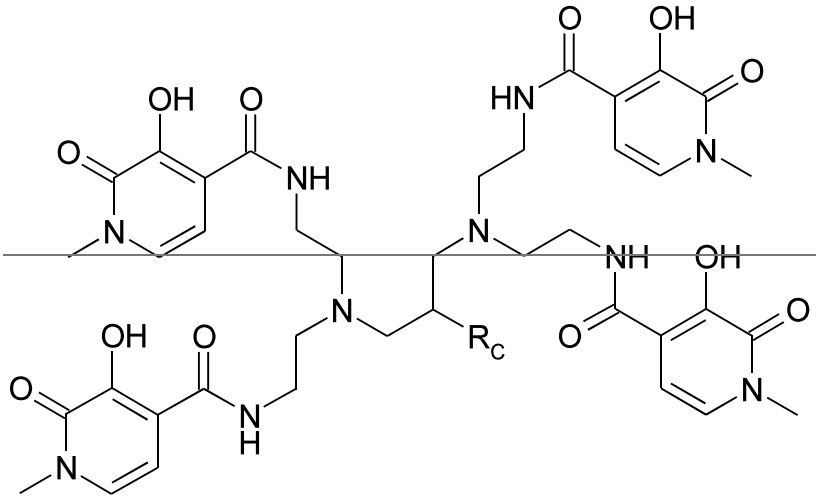
5. The method of any preceding claim wherein step b) is conducted in aqueous solution at pH between 4 and 9.

6. The method of any preceding claim wherein step b) is conducted between 15 and 50°C for 5 to 120 minutes.

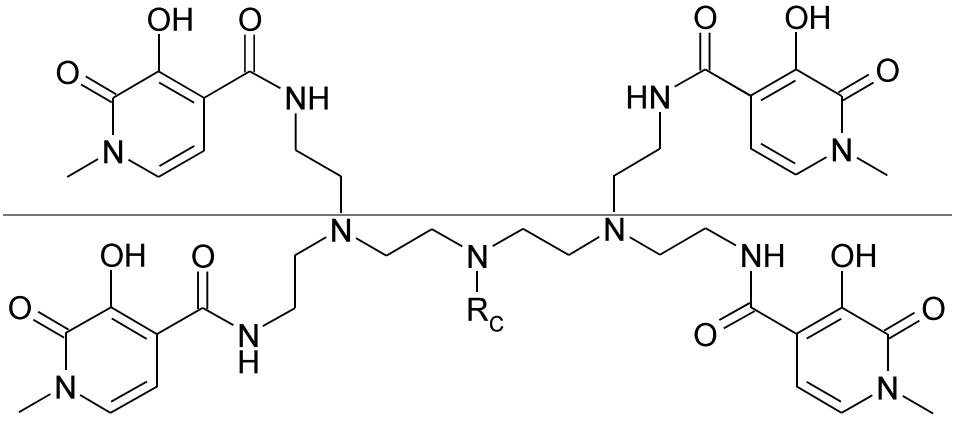
7. The method of any preceding claim wherein step c) is conducted between 15 and 50°C for 1 to 60 minutes.

8. The method of any preceding claim wherein said octadentate chelator comprises four 3,2-HOPO moieties.

9. The method of any preceding claim wherein said octadentate chelator is selected from formulae (VIb) and (VII):



(VIb)



(VII)

wherein Rc is a linker moiety terminating in a carboxylic acid moiety, such as

~~[-CH_2-Ph-N(H)-C(=O)-CH_2-CH_2-C(=O)OH],~~

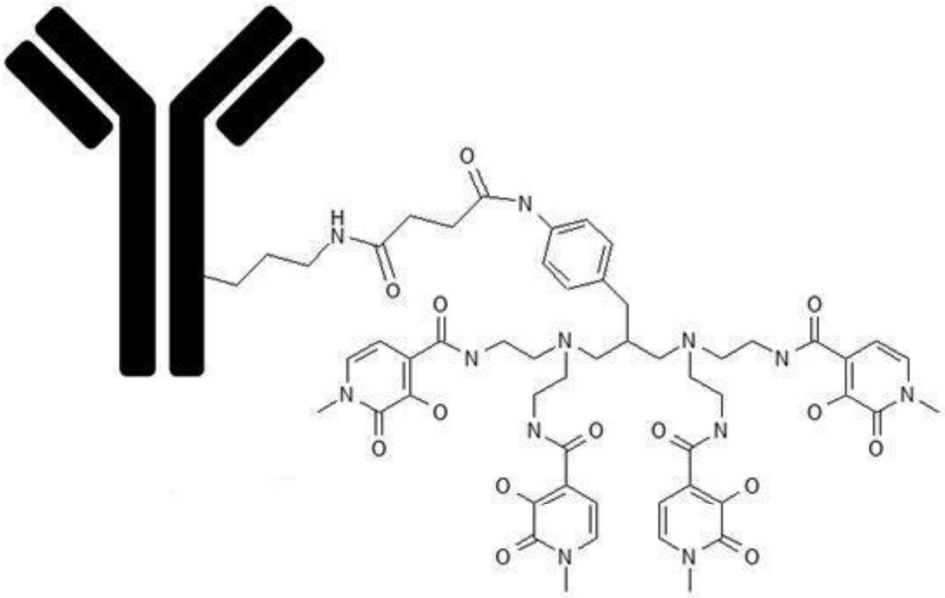
~~[-CH_2-CH_2-N(H)-C(=O)-(CH_2-CH_2-O)$_{1-3}$-CH_2-CH_2-C(=O)OH] or~~

~~[-(CH_2)$_{1-3}$-Ph-N(H)-C(=O)-(CH_2)$_{1-5}$-C(=O)OH],~~

~~wherein Ph is a phenylene group, preferably a para-phenylene group.~~

~~10. The method of any preceding claim wherein said tissue-targeting moiety is a monoclonal or polyclonal antibody, an antibody fragment (such as Fab, F(ab')$_2$, Fab' or scFv), or a construct of such antibodies and/or fragments.~~

1. A tissue-targeting thorium complex comprising the compound:



wherein



represents a tissue targeting moiety comprising at least one peptide or protein having binding affinity for the CD22 receptor, FGFR2, HER-2, PSMA or CD33; and

the 4+ ion of an alpha-emitting thorium radionuclide.

211. The ~~method of any preceding claim wherein said~~ tissue-targeting moiety has binding affinity ~~for the CD22 receptor, FGFR2, Mesothelin,~~ HER-2~~, PSMA or CD33~~.

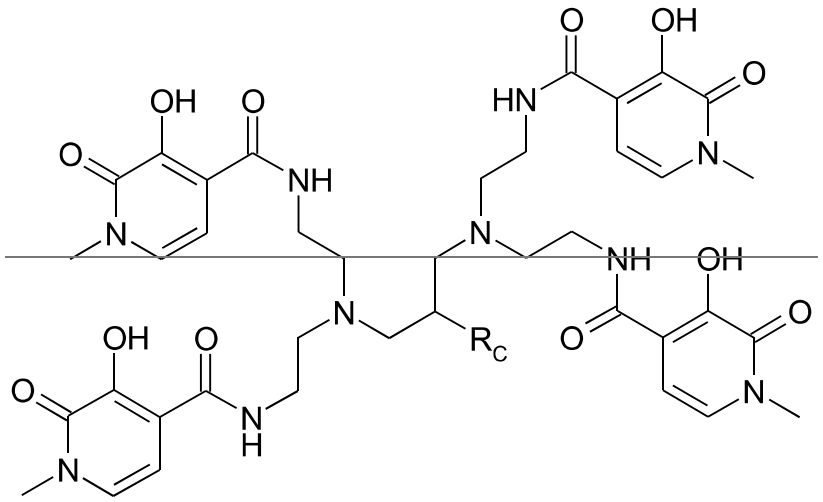
~~12. A tissue-targeting thorium complex formed or formable by the method of any of claims 1 to 11.~~

~~13. The tissue-targeting thorium complex of claim 12 comprising four 3,2-HOPO moieties.~~

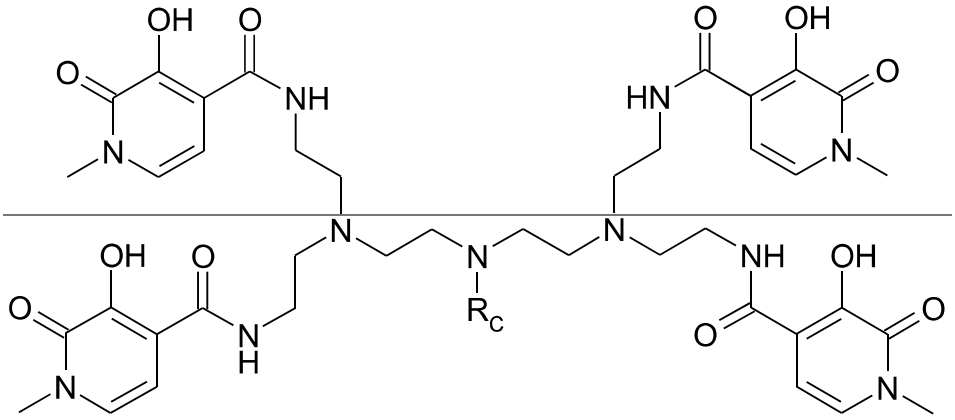
~~14. The tissue-targeting thorium complex of claim 12 or claim 13 having binding affinity for the CD22 receptor, FGFR2, Mesothelin, HER-2, PSMA or CD33.~~

~~15 The tissue-targeting thorium complex of any of claims 12 to 14 comprising the 4+ ion of an alpha-emitting thorium radionuclide such as ^{227}Th.~~

~~16. The tissue-targeting thorium complex of any of claims 12 to 15 comprising an octadentate chelator of formula (VIb) or (VII):~~



(VIb)



(VII)

wherein R_C is a coupling moiety joined by an amide group to a tissue targeting moiety, preferably AGC0019.

17. The tissue-targeting thorium complex of any of claims 12 to 16 comprising a tissue targeting moiety selected from a monoclonal or polyclonal antibody, an antibody fragment (such as Fab, $F(ab')_2$, Fab' or scFv), or a construct of such antibodies and/or fragments.

18 The tissue-targeting thorium complex of any of claims 12 to 17 comprising a tissue targeting moiety comprising at least one peptide chain having at least 90% sequence similarity with at least one of the following sequences:

~~Light Chain:~~

~~DIQLTQSPSSLAVSAGENVTMSC**KSSQSVLYSANHKNYLA**WYQQKPGQSPKLLIY **WASTRES**GVPDRFTGSGSGTDFTLTISRVQVEDLAIYYC**HQYLSSWT**FGGGTKLEI KR (SeqID1)~~

~~DIQLTQSPSSLASAAVEDRTMSC**KSSQSVLYSANHKNYLA**WYQQKPGQKAKLLIY **WASTRES**GVPSRFSGSGSGTDFTFTISSLQPEDIATYYC**HQYLSSWT**FGGGTKLEI KR (SeqID2)~~

~~Heavy Chain:~~

~~QVQLQESGAELSKPGASVKMSCKASGYTFT**SYWLH**WIKQRPGQGLEWIG**YINPRN DYTEYNQNFKD**KATLTADKSSSTAYMQLSSLTSEDSAVYYCAR**RDITTFY**WGQGTT LTVSS (SeqID3)~~

~~QVQLQQSGAEVKKPGSSVKVSCKASGYTFT**SYWLH**WVRQAPGQGLEWIG**YINPR NDYTEYNQNFKD**KATITADESTNTAYMELSSLRSEDTAFYFCAR**RDITTFY**WGQGT TVTVSS (SeqID4)~~

~~QVQLVQSGAEVKKPGSSVKVSCKASGYTFT**SYWLH**WVRQAPGQGLEWIG**YINPR NDYTEYNQNFKD**KATITADESTNTAYMELSSLRSEDTAFYFCAR**RDITTFY**WGQGT TVTVSS (SeqID5)~~

3~~19~~. A pharmaceutical formulation comprising at least one tissue-targeting thorium complex as claimed in ~~any of~~ claim~~s~~ 1 or 2 ~~to 18~~.

4~~20~~. The pharmaceutical formulation of claim 3~~19~~ further comprising citrate buffer.

5~~21~~. The pharmaceutical formulation of claim 3~~19~~ or claim 4~~20~~ further comprising p-aminobutyric acid (PABA), and optionally EDTA and/or at least one polysorbate.~~,~~

~~22. Use of a tissue-targeting thorium complex as claimed any of in claims 12 to 18 or a pharmaceutical formulation as claimed in any of claims 19 to 21 in the manufacture of a medicament for the treatment of hyperplastic or neoplastic disease.~~

~~23. Use as claimed in claim 22 wherein said disease is a carcinoma, sarcoma, myeloma, leukemia, lymphoma or mixed type cancer including Non-Hodgkin's Lymphoma or B-~~

~~cell neoplasms, breast, endometrial, gastric, acute myeloid leukemia, prostate or brain, mesothelioma, ovarian, lung or pancreatic cancer~~

~~24. A method of treatment of a human or non-human animal (particularly one in need thereof) comprising administration of at least one tissue-targeting thorium complex as claimed any of in claims 12 to 18 or at least one pharmaceutical formulation as claimed in any of claims 19 to 21.~~

~~25. The method of claim 24 for the treatment of hyperplastic or neoplastic disease, such as a carcinoma, sarcoma, myeloma, leukemia, lymphoma or mixed type cancer, including Non-Hodgkin's Lymphoma or B-cell neoplasms, breast, endometrial, gastric, acute myeloid leukemia, prostate or brain, mesothelioma, ovarian, lung or pancreatic cancer~~

~~2~~6. ~~A tissue-targeting thorium complex as claimed any of in claims 12 to 18 or a~~ The pharmaceutical formulation as claimed in any of claims 3 to 5~~19 to 21~~, for use in the treatment of hyperplastic and/or neoplastic disease such as a carcinoma, sarcoma, myeloma, leukemia, lymphoma or mixed type cancer including Non-Hodgkin's Lymphoma or B-cell neoplasms, breast, endometrial, gastric, acute myeloid leukemia, prostate or brain, mesothelioma, ovarian, lung or pancreatic cancer.

~~27. A kit for use in a method according to any of claims 1 to 11, said kit comprising:~~

~~i) an octadentate chelator comprising four hydroxypyridinone (HOPO) moieties, substituted in the N-position with a C_1-C_3 alkyl group, and coupling moiety terminating in a carboxylic acid group;~~

~~ii) at least one tissue-targeting peptide or protein comprising at least one amine moiety;~~

~~iii) at least one amide-coupling reagent; and~~

iv) optionally and preferably an alpha-emitting thorium radionuclide, such as ^{227}Th.