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(54) Benævnelse: **MÅLRETNINGSKORROLER TIL TUMORTOKSICITET OG MRI**

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DESCRIPTION

RELATED APPLICATIONS

[0001] The present application claims priority to the U.S. Provisional Application Serial No. 61/821,106, filed May 8, 2013.

STATEMENT REGARDING FEDERALLY-SPONSORED RESEARCH

[0002] The U.S. Government has a paid-up license in this invention and the right in limited circumstances to require the patent owner to license others on reasonable terms as provided for by the terms of Grant Nos. CA 129822 and CA 140995 awarded by National Institutes of Health and Grant No. UL1TR000124 awarded by National Center for Advancing Translational Sciences.

FIELD OF INVENTION

[0003] This invention relates to compositions for use in the treatment of cancer and imaging techniques.

BACKGROUND

[0004] The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

[0005] Whereas cancer treatment by porphyrins and related macrocyclic compounds has been investigated extensively for many decades, the therapeutic potential of corroles has only recently been disclosed. Sulfonated corroles are water soluble (amphipolar) macrocyclic compounds, whose Fe(III) and Mn(III) complexes are very active catalysts for decomposition of reactive oxygen and nitrogen species involved in a variety of relevant diseases. Also noteworthy is the finding that Ga(III) and Al(III) derivatives are intensely fluorescent at relatively long wavelengths. While these metal complexes are capable of undergoing endocytosis via co-uptake with, or noncovalent attachment to, serum proteins *in vitro* and *in vivo,* they are unable to penetrate cell membranes without facilitation by membrane-lytic molecules. Hence, toxic corroles, such as the Ga(III) derivative, are safe at pharmacologic doses but can kill cells when allowed to breach into the cytosol.

[0006] The publication of H. Agadjanian et al., "Tumor detection and elimination by a targeted gallium corrole", Proceedings of the National Academy of Sciences, vol. 106, no. 15, pp. 6105-6110 relates to in vivo imaging and therapeutic efficacy of a tumor-targeted gallium corrole noncovalently assembled with a heregulin-modified protein directed at the human epidermal growth factor receptor (HER).

[0007] The publication of D. Pan et al., "Manganese-based MRI contrast agents: past, present, and future", Tetrahedron, vol. 67, no. 44, pp. 8431-8444 describes MRI contrast agent families based on manganese, which involve free ionic manganese, chelated manganese, hybrid manganese agents, macromolecular agents and nanoparticle-based agents.

[0008] The publication of P. Lim et al., "Differential Cytostatic and Cytotoxic Action of Metallocorroles against Human Cancer Cells: Potential Platforms for Anticancer Drug Development", Chemical Research in Toxicology, vol. 25, no. 2, pp. 400-409 relates to a gallium(III)-substituted amphiphilic corrole noncovalently associated with a targeting protein, which has cytotoxic and antitumor activities.

[0009] The publication of H. Agadjanian, "Specific Delivery of Corroles to Cells via Noncovalent Conjugates with Viral Proteins", Pharmaceutical Research, vol. 23, no. 2, pp. 367-377 describes tests of corroles mixed with recombinant proteins for conjugate assembly, cell penetration, stability, targeted binding and cell killing in vitro.

SUMMARY OF THE INVENTION

[0010] Disclosed herein are compositions comprising a targeted corrole nanoparticle; and an acceptable excipient. Also disclosed are compositions comprising a targeted corrole nanoparticle; and an acceptable carrier. Further, disclosed herein are methods of imaging a condition in a subject, comprising providing a composition comprising a targeted corrole nanoparticle; administering an effective amount of the targeted corrole nanoparticle to the subject; and imaging the condition in the subject. In addition, disclosed herein are methods of treating cancer in a subject, comprising providing a composition comprising a targeted corrole nanoparticle; and administering a therapeutically effective dosage of the targeted corrole nanoparticle to the subject.

[0011] Accordingly, the present invention as set out in the appended claims relates to a pharmaceutical composition for use in the treatment of cancer, comprising a targeted nanoparticle comprising a targeting protein and a metallated corrole comprising manganese; and a pharmaceutically acceptable excipient;
wherein the targeted nanoparticle targets a tumor.

[0012] In some embodiments, the pharmaceutical composition for use is for further use in imaging by MRI.

[0013] In some embodiments the targeting protein is a recombinant tumor-targeted cell penetration protein, and wherein the nanoparticle is formed by a noncovalent assembly of the recombinant tumor-targeted cell penetration protein with a water-soluble sulfonated corrole forming a round virus-like particle of 10-20 nm in diameter.

[0014] In some embodiments the targeting protein is a HerPBK10 molecule.

[0015] In some embodiments the metallated corrole is sulfonated.

[0016] In some embodiments the metallated corrole is S2Mn.

[0017] In some embodiments the targeting protein is a HerPBK10 molecule, and wherein the targeted nanoparticle targets a HER2+ tumor.

[0018] In some embodiments the pharmaceutical composition is formulated for aerosol, nasal, oral, transmucosal, transdermal, or parenteral administration.

[0019] The present invention also relates to a use of a composition for imaging a tumor by MRI, characterized by the composition comprising a targeted nanoparticle comprising a targeting protein and a metallated corrole comprising manganese; and a pharmaceutically acceptable excipient;

wherein the targeted nanoparticle targets a tumor, and

wherein the targeting protein is a HerPBK10 molecule.

[0020] In some embodiments of the use the metallated corrole is sulfonated.

[0021] In some embodiments of the use the metallated corrole is S2Mn.

[0022] In some embodiments of the use the targeted nanoparticle targets a HER2+ tumor.

[0023] In some embodiments of the use the pharmaceutical composition is formulated for aerosol, nasal, oral, transmucosal, transdermal, or parenteral administration.

[0024] The present invention also relates to a use of a composition for imaging a tumor by MRI, characterized by the composition comprising a targeted nanoparticle comprising a targeting protein and a metallated corrole comprising manganese; and a pharmaceutically acceptable excipient;

wherein the targeted nanoparticle targets a tumor,

wherein the targeting protein is a recombinant tumor-targeted cell penetration protein, and

wherein the nanoparticle is formed by a noncovalent assembly of the recombinant tumor-targeted cell penetration protein with a water-soluble sulfonated corrole forming a round virus-like particle of 10-20 nm in diameter.

[0025] Further embodiments of the invention are described throughout the present description.

BRIEF DESCRIPTION OF THE FIGURES

[0026] Exemplary embodiments are illustrated in referenced figures. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

Figure 1 depicts, in accordance with an embodiment herein, measuring TI relaxation time of Mn, Fe, and Ga corroles. Different concentrations of each corrole were prepared and measured in situ (in a microfuge tube) for TI relaxation time.

Figure 2 depicts, in accordance with an embodiment herein, assembly of HerMn.

Figure 3 depicts, in accordance with an embodiment herein, tumor-toxicity of HerMn. HerMn was injected (5 nmoles per injection) into the tail vein of female nude mice bearing bilateral flank tumors of human HER2+ cancer cells. Mice received daily injections, 1 x/day for 7 days, while tumors were monitored for growth by measuring volumes using calipers on a regular basis. Control injections included equivalent doses of untargeted corrole (S2Mn), HerPBK10, and vehicle alone (saline). A, Growth plots of tumor volumes from treated mice. N=6-8 tumors per sample. B, Mice treated with saline (left mouse) or HerMn (right mouse). Arrows point to tumors. C, MRI of tumor from HerMn-treated mouse on the day of the last injection (Day 0) and 30 days later (Day 30). Tumor is indicated by the arrow. The MRI shows tumor volume without the use of a contrast agent.

Figure 4 depicts, in accordance with an embodiment herein, TI time reduction and MRI contrast of S2Mn in vivo. Female nude mice bearing bilateral flank xenografts of human HER2+ tumors received intratumoral injections of S2Mn or saline at the indicated doses. A, TI relaxation time measurements obtained from the tumors of live mice. B, MRI of tumors in live mice before (left image) and after (right image) injections of either HerMn (1 mmole) or saline (indicated by left and right arrows, respectively).

DESCRIPTION OF THE INVENTION

[0027] Unless defined otherwise, technical and scientific terms used herein have the same

meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton et al., Dictionary of Microbiology and Molecular Biology 3rd ed., J. Wiley & Sons (New York, NY 2001); March, Advanced Organic Chemistry Reactions, Mechanisms and Structure 5th ed., J. Wiley & Sons (New York, NY 2001); and Sambrook and Russel, Molecular Cloning: A Laboratory Manual 3rd ed., Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY 2001), provide one skilled in the art with a general guide to many of the terms used in the present application. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention.

[0028] As used herein, "treatment" or "treating" should be understood to include any indicia of success in the treatment, alleviation or amelioration of an injury, pathology or condition. This may include parameters such as abatement, remission, diminishing of symptoms, slowing in the rate of degeneration or decline, making the final point of degeneration less debilitating; improving a patient's physical or mental well-being; or, preventing the onset of disease.

[0029] Disclosed herein within the context of the invention are tumor-targeted protein-based nanoparticles that are capable of both imaging and tumor detection, as well as tumor treatment. The nanoparticle may be the combination of metallated corroles, specifically manganese (Mn), iron (Fe), or gallium (Ga), and HerPBK10 molecules, resulting in a HerMn, HerFe, or HerGa nanoparticle, respectively. As further disclosed herein, studies demonstrated that HerGa only allowed tumor detection when tumors were localized within several centimeters under the skin, and that thus usage of HerGa for tumor detection may require more advanced imaging methodologies than MRI. Studies also demonstrated that HerMn exhibited greater potential as an imaging agent for MRI as compared to HerFe. Additional studies focused on HerMn, finding that in addition to being a suitable imaging agent for MRI, HerMn exhibited significant inhibition of tumor growth in vivo.

[0030] HerPBK10 is defined and described in the art, for example in U.S. Patent Application Publication No. US 2012/0004181 A1, specifically at Paragraph [0063].

[0031] Disclosed herein within the context of the invention are methods of treating cancer in a subject by providing a composition comprising a tumor targeted corrole nanoparticle, and administering a therapeutically effective dosage of the composition to the subject. The tumor targeted corrole nanoparticle may include manganese (Mn), iron (Fe), and/or gallium (Ga). The nanoparticle may be the combination of a corrole compound with a HerPBK10 molecule. The nanoparticle may be HerMn, HerFe, or HerGa.

[0032] Disclosed herein within the context of the invention are methods of imaging cancer in a subject by providing a composition comprising a tumor targeted corrole nanoparticle, and administering an effective dosage of the composition to the subject. The tumor targeted corrole nanoparticle may include manganese (Mn), iron (Fe), and/or gallium (Ga). The nanoparticle is the combination of a corrole compound with a HerPBK10 molecule. The nanoparticle may be HerMn, HerFe, or HerGa. In another embodiment, the imaging is performed by MRI.

[0033] Disclosed herein within the context of the invention are methods of imaging and diagnosing a disease in a subject by providing a composition comprising a targeted corrole nanoparticle, administering an effective dosage of the composition to the subject, and diagnosing the disease based on imaging of the subject. The targeted corrole nanoparticle may include manganese (Mn), iron (Fe), and/or gallium (Ga). The nanoparticle may be the combination of a corrole compound with a HerPBK10 molecule. The nanoparticle may be HerMn, HerFe, or HerGa. The imaging may be performed by MRI.

[0034] Disclosed herein within the context of the invention are methods of imaging and treating a disease in a subject by providing a composition comprising a targeted corrole nanoparticle, administering an effective dosage of the composition to the subject, and imaging and treating the subject. The targeted corrole nanoparticle may include manganese (Mn), iron (Fe), and/or gallium (Ga). The nanoparticle may be the combination of a corrole compound with a HerPBK10 molecule. The nanoparticle may be HerMn, HerFe, or HerGa. The imaging may be performed by MRI.

[0035] Disclosed herein within the context of the invention are compositions comprising a targeted corrole nanoparticle. The targeted corrole nanoparticle may include manganese (Mn), iron (Fe), and/or gallium (Ga). The nanoparticle may be the combination of a corrole compound with a HerPBK10 molecule. The nanoparticle may be HerMn, HerFe, or HerGa. The imaging may be performed by MRI.

[0036] Disclosed herein within the context of the invention are pharmaceutical compositions including a pharmaceutically acceptable excipient along with a therapeutically effective amount of a targeted corrole nanoparticle. "Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for veterinary use as well as for human pharmaceutical use. Such excipients may be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous.

[0037] In various embodiments, the pharmaceutical compositions may be formulated for delivery via any route of administration. "Route of administration" may refer to any administration pathway known in the art, including but not limited to aerosol, nasal, oral, transmucosal, transdermal or parenteral. "Parenteral" refers to a route of administration that is generally associated with injection, including intraorbital, infusion, intraarterial, intracapsular, intracardiac, intradermal, intramuscular, intraperitoneal, intrapulmonary, intraspinal, intrasternal, intrathecal, intrauterine, intravenous, subarachnoid, subcapsular, subcutaneous, transmucosal, or transtracheal. Via the parenteral route, the compositions may be in the form of solutions or suspensions for infusion or for injection, or as lyophilized powders.

[0038] The pharmaceutical compositions disclosed herein can also contain any pharmaceutically acceptable carrier. "Pharmaceutically acceptable carrier" as used herein refers to a pharmaceutically acceptable material, composition, or vehicle that is involved in

carrying or transporting a compound of interest from one tissue, organ, or portion of the body to another tissue, organ, or portion of the body. For example, the carrier may be a liquid or solid filler, diluent, excipient, solvent, or encapsulating material, or a combination thereof. Each component of the carrier must be "pharmaceutically acceptable" in that it must be compatible with the other ingredients of the formulation. It must also be suitable for use in contact with any tissues or organs with which it may come in contact, meaning that it must not carry a risk of toxicity, irritation, allergic response, immunogenicity, or any other complication that excessively outweighs its therapeutic benefits.

[0039] The pharmaceutical compositions can also be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, alcohols and water. Solid carriers include starch, lactose, calcium sulfate, dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax.

[0040] The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

[0041] The pharmaceutical compositions may be delivered in a therapeutically effective amount. The precise therapeutically effective amount is that amount of the composition that will yield the most effective results in terms of efficacy of treatment in a given subject. This amount will vary depending upon a variety of factors, including but not limited to the characteristics of the therapeutic compound (including activity, pharmacokinetics, pharmacodynamics, and bioavailability), the physiological condition of the subject (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage, and type of medication), the nature of the pharmaceutically acceptable carrier or carriers in the formulation, and the route of administration. One skilled in the clinical and pharmacological arts will be able to determine a therapeutically effective amount through routine experimentation, for instance, by monitoring a subject's response to administration of a compound and adjusting the dosage accordingly. For additional guidance, see Remington: The Science and Practice of Pharmacy (Gennaro ed. 20th edition, Williams & Wilkins PA, USA) (2000).

[0042] Typical dosages of an effective targeted corrole nanoparticle can be in the ranges recommended by the manufacturer where known therapeutic compounds are used, and also as indicated to the skilled artisan by the *in vitro* responses or responses in animal models. Such dosages typically can be reduced by up to about one order of magnitude in concentration or amount without losing the relevant biological activity. Thus, the actual dosage will depend

upon the judgment of the physician, the condition of the patient, and the effectiveness of the therapeutic method based, for example, on the *in vitro* responsiveness of the relevant primary cultured cells or histocultured tissue sample, such as biopsied malignant tumors, or the responses observed in the appropriate animal models, as previously described.

[0043] The various methods and techniques described above provide a number of ways to carry out the invention. Of course, it is to be understood that not necessarily all objectives or advantages described may be achieved in accordance with any particular embodiment described herein. Thus, for example, those skilled in the art will recognize that the methods can be performed in a manner that achieves or optimizes one advantage or group of advantages as taught herein without necessarily achieving other objectives or advantages as may be taught or suggested herein. A variety of advantageous and disadvantageous alternatives are mentioned herein. It is to be understood that some preferred embodiments specifically include one, another, or several advantageous features, while others specifically exclude one, another, or several disadvantageous features, while still others specifically mitigate a present disadvantageous feature by inclusion of one, another, or several advantageous features.

[0044] Furthermore, the skilled artisan will recognize the applicability of various features from different embodiments. Similarly, the various elements, features and steps discussed above, as well as other known equivalents for each such element, feature or step, can be mixed and matched by one of ordinary skill in this art to perform methods in accordance with principles described herein. Among the various elements, features, and steps some will be specifically included and others specifically excluded in diverse embodiments.

[0045] Although the invention has been disclosed in the context of certain embodiments and examples, it will be understood by those skilled in the art that the embodiments of the invention extend beyond the specifically disclosed embodiments to other alternative embodiments and/or uses and modifications and equivalents thereof.

[0046] Many variations and alternative elements have been disclosed in embodiments of the present invention. Still further variations and alternate elements will be apparent to one of skill in the art. Among these variations, without limitation, are the selection of constituent modules for the inventive compositions, and the diseases and other clinical conditions that may be diagnosed, prognosed or treated therewith. Various embodiments of the invention can specifically include or exclude any of these variations or elements.

[0047] In some embodiments, the numbers expressing quantities of ingredients, properties such as concentration, reaction conditions, and so forth, used to describe and claim certain embodiments of the invention are to be understood as being modified in some instances by the term "about." Accordingly, in some embodiments, the numerical parameters set forth in the written description and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by a particular embodiment. In some embodiments, the numerical parameters should be construed in light of the number of reported significant

digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of some embodiments of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as practicable. The numerical values presented in some embodiments of the invention may contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[0048] In some embodiments, the terms "a" and "an" and "the" and similar references used in the context of describing a particular embodiment of the invention (especially in the context of certain of the following claims) can be construed to cover both the singular and the plural. The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided with respect to certain embodiments herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0049] Groupings of alternative elements or embodiments of the invention disclosed herein are not to be construed as limitations. Each group member can be referred to and claimed individually or in any combination with other members of the group or other elements found herein. One or more members of a group can be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is herein deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0050] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations on those preferred embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. It is contemplated that skilled artisans can employ such variations as appropriate, and the invention can be practiced otherwise than specifically described herein. Accordingly, many embodiments of this invention include all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0051] Furthermore, numerous references have been made to patents and printed publications throughout this specification.

[0052] In closing, it is to be understood that the embodiments of the invention disclosed herein

are illustrative of the principles of the present invention. Other modifications that can be employed can be within the scope of the invention. Thus, by way of example, but not of limitation, alternative configurations of the present invention can be utilized in accordance with the teachings herein. Accordingly, embodiments of the present invention are not limited to that precisely as shown and described. The scope of protection is determined by the appended claims.

EXAMPLES

[0053] The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention.

Example 1

Mn-corrole shows highest TI relaxation time in vitro.

[0054] The inventors assessed an initial panel of corroles to determine which, if any, exhibit potential as a contrast agent for MRI. To determine this, the inventors measured the TI time reduction of each at increasing concentrations, under in vitro conditions. Of the three corroles measured (gallium, iron, and manganese - metallated compounds), the Mn corrole, S2Mn, exhibited the largest TI time shortening (Figure 1). Subsequent studies were therefore performed using this compound.

Example 2

Targeted Mn-corrole, HerMn, kills tumors in vivo.

[0055] The inventors examined whether S2Mn was toxic to tumors when delivered by the targeting protein, HerPBK10. The particle resulting from the non-covalent interaction between S2Mn and HerPBK10 (called HerMn; Figure 2) was tested for tumor-targeted toxicity in an in vivo xenograft mouse model of human HER2+ cancer. We delivered HerMn at 5 nmoles per injection or the equivalent dose of S2Mn alone, HerPBK10 alone, and saline, via tail vein injection daily for 7 days, and monitored tumor growth for 25 days following the final injection. This study showed that HerMn can cause tumor growth ablation in vivo whereas the individual components do not (Figure 3).

Example 3

S2Mn exhibits TI time shortening and MRI contrast in vivo.

[0056] To determine whether S2Mn exhibited contrast by MRI, the inventors measured the TI time shortening of S2Mn in vivo after intratumoral injection at different doses per injection. An accumulation of 100 umoles S2Mn in the tumor yielded a significant difference in TI time shortening compared to the equivalent volume of saline injected into the contralateral tumor (Figure 4A). However, 1 mmole S2Mn produced a better TI time reduction that could be better distinguished from background tissue signals (Figure 4A), and likewise yielded a detectable contrast by MRI (Figure 4B).

[0057] Taken altogether, the findings demonstrate that HerMn is a viable agent for both targeted tumor killing and detection via MRI. These findings support translation of HerMn toward future clinical application.

Example 4

Overview

[0058] As disclosed herein, the inventors developed a tumor-targeted protein-based nanoparticle capable of simultaneous tumor detection and treatment. In one embodiment, the nanoparticle is formed by noncovalent assembly of a recombinant tumor-targeted cell penetration protein (HerPBK10) with water-soluble sulfonated corroles, forming round virus-like particles of 10-20 nm diameter. While HerPBK10 facilitates tumor targeting and cell membrane penetration, the corrole noncovalently binds to the protein and enables detection and cytotoxicity. The inventors demonstrated that that delivery of a gallium-metallated corrole by HerPBK10 (resulting in the complex, HerGa) can emit an intense red fluorescence to track tumor-targeting while selectively killing HER2+ tumors. However, tumor detection using HerGa is only allowed when tumors are localized within several centimeters under the skin since the penetration depths of light are limited to several centimeters. Thus, the usage of HerGa for tumor detection in the clinic may require more advanced imaging methodologies including endoscopic technologies. As disclosed herein, the inventors have explored whether alternative metallated corroles can be used that, when combined with HerPBK10, are as cytotoxic as HerGa but bear sufficient contrast properties to enable detection using clinically relevant devices such as MRI. The inventors examined whether tumor-targeted particles carrying manganese (Mn) and iron (Fe) corroles (HerMn or HerFe, respectively) bear sufficient contrast for MRI while sustaining targeted-toxicity to HER2+ tumor cells *in vivo.*

[0059] Various embodiments of the invention are described above in the Detailed Description. While these descriptions directly describe the above embodiments, it is understood that those skilled in the art may conceive modifications and/or variations to the specific embodiments shown and described herein. Any such modifications or variations that fall within the purview of this description are intended to be included therein as well. Unless specifically noted, it is the intention of the inventors that the words and phrases in the specification and claims be given the ordinary and accustomed meanings to those of ordinary skill in the applicable art(s).

[0060] The foregoing description of various embodiments of the invention known to the applicant at this time of filing the application has been presented and is intended for the purposes of illustration and description. The present description is not intended to be exhaustive nor limit the invention to the precise form disclosed and many modifications and variations are possible in the light of the above teachings. The embodiments described serve to explain the principles of the invention and its practical application and to enable others skilled in the art to utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. Therefore, it is intended that the invention not be limited to the particular embodiments disclosed for carrying out the invention.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US61821106 [0001]
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Cancer Cells: Potential Platforms for Anticancer Drug DevelopmentChemical Research in Toxicology, vol. 25, 2400-409 [0008]

- **H. AGADJANIAN**Specific Delivery of Corroles to Cells via Noncovalent Conjugates with Viral ProteinsPharmaceutical Research, vol. 23, 2367-377 [0009]
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Patentkrav

1. Farmaceutisk sammensætning til anvendelse i behandlingen af cancer, omfattende en målrettet nanopartikel omfattende et målretningsprotein og en metalleret korrol omfattende mangan; og et farmaceutisk acceptabelt hjælpestof; hvor den målrettede nanopartikel er rettet mod en tumor.

2. Farmaceutisk sammensætning til anvendelse ifølge krav 1, til yderligere anvendelse i billeddannelse med MRI.

3. Farmaceutisk sammensætning til anvendelse ifølge krav 1 eller krav 2, hvor målretningsproteinet er et rekombinant tumor-målrettet cellepenetrerende protein, og hvor nanopartiklen er dannet af en ikke-kovalent samling af det rekombinante tumor-målrettede cellepenetrerende protein med en vandopløselig sulfoneret korrol, der danner en rund virus-lignende partikel på 10-20 nm i diameter.

4. Farmaceutisk sammensætning til anvendelse ifølge krav 1 eller 2, hvor målretningsproteinet er et HerPBK10-molekyle.

5. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst af kravene 1, 2 og 4, hvor den metallerede korrol er sulfoneret.

6. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst af kravene 1, 2, 4 og 5, hvor den metallerede korrol er S2Mn.

7. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst af kravene 1-6, hvor målretningsproteinet er et HerPBK10-molekyle, og hvor den målrettede nanopartikel er rettet mod en HER2+-tumor.

8. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst af kravene 1-7, hvor den farmaceutiske sammensætning er formuleret til aerosol, nasal, oral, transmucosal, transdermal eller parenteral indgivelse.

9. Anvendelse af en sammensætning til billeddannelse af en tumor med MRI, **kendetegnet ved, at** sammensætningen omfatter en målrettet nanopartikel omfattende et målretningsprotein og en metalleret korrol omfattende mangan; og et farmaceutisk acceptabelt hjælpestof;

hvor den målrettede nanopartikel er rettet mod en tumor, og
hvor målretningsproteinet er et HerPBK10-molekyle.

10. Anvendelse af sammensætningen ifølge krav 9, hvor den metallerede korrol er sulfoneret.

11. Anvendelse af sammensætningen ifølge krav 9 eller 10, hvor den metallerede korrol er S2Mn.

12. Anvendelse af sammensætningen ifølge et hvilket som helst af kravene 9-11, hvor den målrettede nanopartikel er rettet mod en HER2+-tumor.

13. Anvendelse af sammensætningen ifølge et hvilket som helst af kravene 9-12, hvor den farmaceutiske sammensætning er formuleret til aerosol, nasal, oral, transmucosal, transdermal eller parenteral indgivelse.

14. Anvendelse af en sammensætning til billeddannelse af en tumor med MRI, **kendetegnet ved, at** sammensætningen omfatter en målrettet nanopartikel omfattende et målretningsprotein og en metalleret korrol omfattende mangan; og et farmaceutisk acceptabelt hjælpestof;

hvor den målrettede nanopartikel er rettet mod en tumor,
hvor målretningsproteinet er et rekombinant tumor-målrettet cellepenetrerende protein, og hvor nanopartiklen er dannet af en ikke-kovalent samling af det rekombinante tumor-målrettede cellepenetrerende protein med en vandopløselig sulfoneret korrol, der danner en rund virus-lignende partikel på 10-20 nm i diameter.

DRAWINGS

Figure 1.

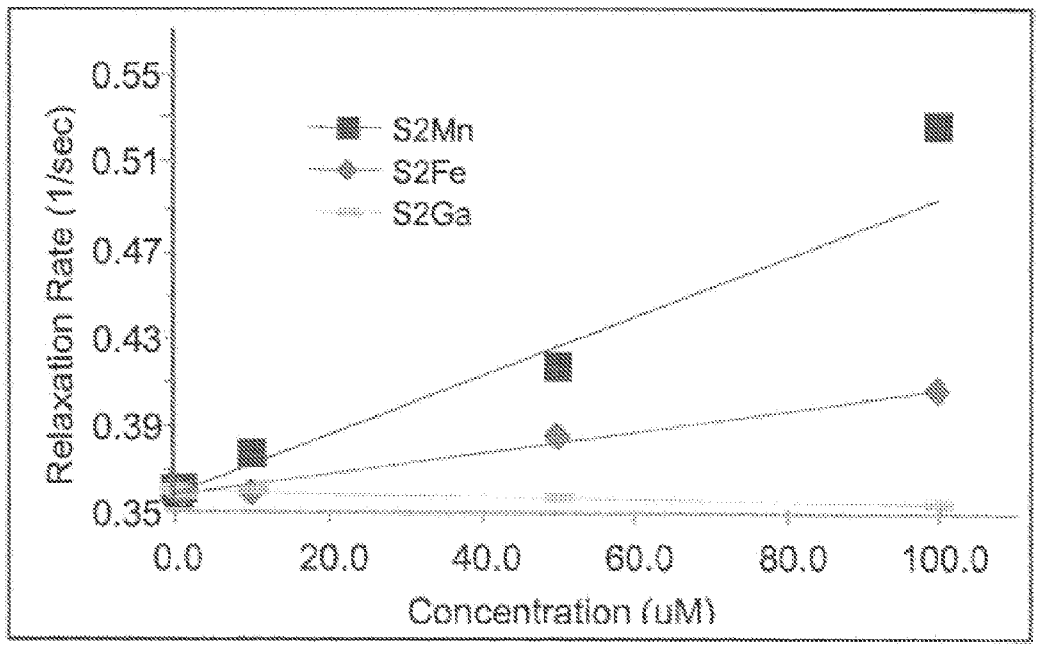


Figure 2.

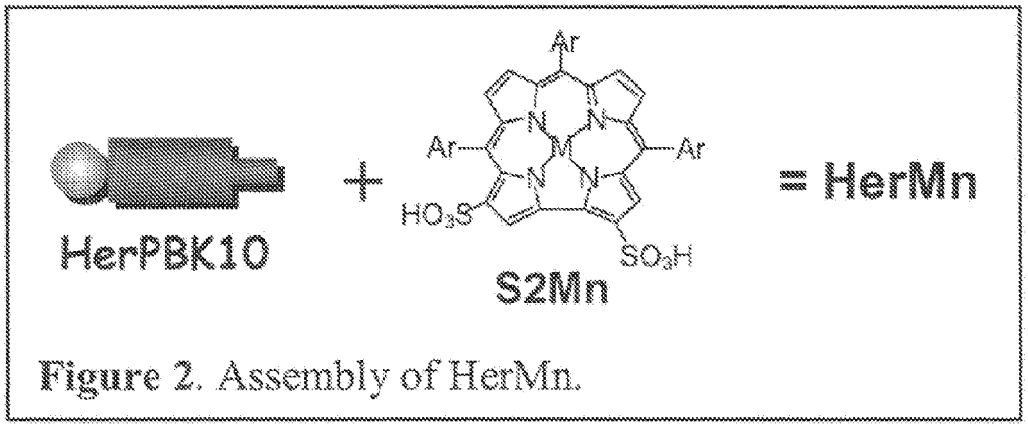


Figure 2. Assembly of HerMn.

Figure 3.

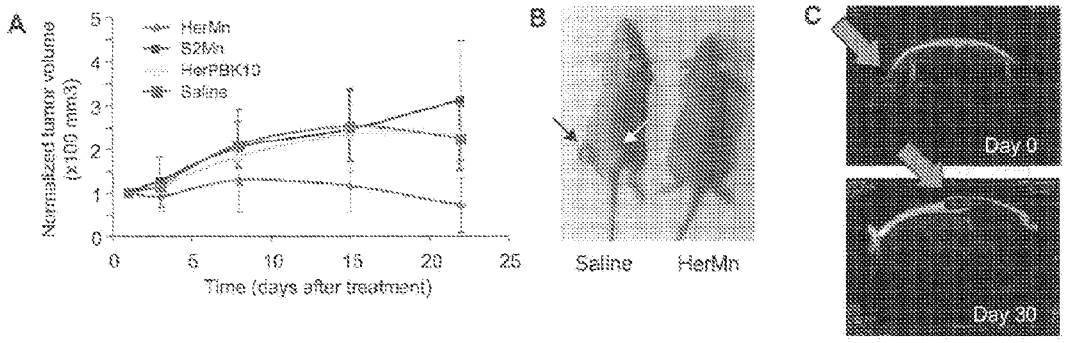
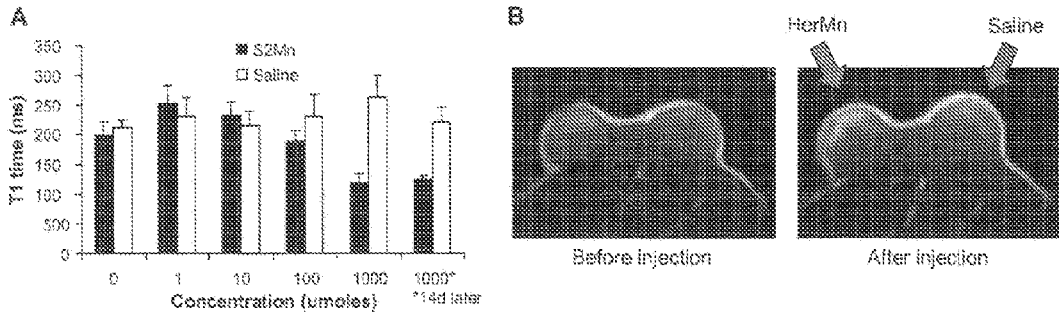


Figure 4.


A
S2Mn
Saline
T1 time (ms)
350
300
250
200
150
100
50
0
0
1
10
100
1000
1000*
Concentration (umoles)
*14d later
B
HerMn
Saline
Before injection
After injection