2006;47:1144–1152.; Schroeder RP et al. *Eur J Nucl Med Mol Imaging.* 2010;37:1386–1396.; Nock B, et al. *Eur J Nucl Med Mol Imaging.* 2003;30:247–258.; Mather SJ, et al. *Mol Imaging Biol.* 2014;16:888–895). Recent studies have shown a preference for GRPR antagonists compared with GRPR agonists (Mansi R, et al. *Eur J Nucl Med Mol Imaging.* 2011;38:97–107; Cescato R, et al. *J Nucl Med.* 2008;49:318–326). Compared with receptor agonists, antagonists often show higher binding and favorable pharmacokinetics (Ginj M, et al. *Proc Natl Acad Sci USA.* 2006;103:16436–16441). Also, clinical studies with radiolabeled GRPR agonists reported unwanted side effects in patients caused by activation of the GRPR after binding of the peptide to the receptor (Bodei L, et al. [abstract]. *Eur J Nucl Med Mol Imaging.* 2007;34:S221).

It was recently found that some GRPR-antagonists, like NeoBOMB1, can be radiolabeled with different radionuclides and could potentially be used for imaging and for treating GRPR-expressing cancers, for example but not limited to, prostate cancer and breast cancer. However, only biodistribution studies have been reported so far and no efficient treatment protocol or pharmaceutical compositions have been developed.

In this context, it would thus be desirable to provide a pharmaceutical composition comprising a GRPR-antagonist which could be administrated to patients. Moreover, it would also be desirable to provide an efficient treatment protocol for patients with cancer using a GRPR-antagonist.

SUMMARY

In one aspect, the present disclosure refers to a pharmaceutical composition comprising

- a radiolabeled GRPR-antagonist of the following formula:

  MC- S - P

  wherein :

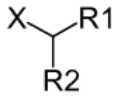
  M is a radiometal and C is a chelator which binds M;

  S is an optional spacer covalently linked between C and the N-terminal of P;

  P is a GRP receptor peptide antagonist of the general formula :

  Xaa1-Xaa2—Xaa3—Xaa4 —Xaa5—Xaa6—Xaa7—Z;

Xaa1 is not present or is selected from the group consisting of amino acid residues Asn, Thr, Phe, 3- (2-thienyl) alanine (Thi), 4-chlorophenylalanine (Cpa) , α-naphthylalanine (α-Nal) , β-naphthylalanine (β-Nal) , 1,2,3,4-tetrahydronorharman-3-carboxylic acid (Tpi), Tyr, 3-iodo-tyrosine (o-I-Tyr) , Trp and pentafluorophenylalanine (5-F-Phe) (all as L- or D-isomers) ;
Xaa2 is Gln, Asn or His;
Xaa3 is Trp or 1, 2, 3, 4-tetrahydronorharman-3-carboxylic acid (Tpi);
Xaa4 is Ala, Ser or Val;
Xaa5 is Val, Ser or Thr;
Xaa6 is Gly, sarcosine (Sar), D-Ala, or β-Ala;
Xaa7 is His or (3-methyl)histidine (3-Me)His;
Z is selected from -NHOH, -NHNH2, -NH-alkyl, -N(alkyl)2, and -O-alkyl
or Z is



wherein X is NH (amide) or O (ester) and R1 and R2 are the same or different and selected from a proton, an optionally substituted alkyl, an optionally substituted alkyl ether, an aryl, an aryl ether or an alkyl-, halogen, hydroxyl or hydroxyalkyl substituted aryl or heteroaryl group; and

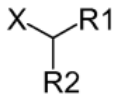
- a surfactant comprising a compound having (i) a polyethylene glycol chain and (ii) a fatty acid ester.

In another aspect, the present disclosure refers to the pharmaceutical composition as disclosed herein, for use in treating or preventing cancer. In another aspect, the present disclosure refers to the pharmaceutical composition as disclosed herein, for use in in vivo imaging, preferably PET and SPECT imaging.

In yet another aspect, the present disclosure refers to a use of a composition as disclosed herein in the manufacture of a medicament for treating or preventing cancer. In another example, the present disclosure describes a composition comprising a radiolabeled GRPR-antagonist for use in treating or preventing cancer in a subject, wherein

- the radiolabeled GRPR-antagonist is of the following formula:
  MC- S - P
  wherein :
  M is a radiometal and C is a chelator which binds M;
  S is an optional spacer covalently linked between C and the N-terminal of P;
  P is a GRP receptor peptide antagonist of the general formula :
  Xaa1-Xaa2—Xaa3—Xaa4 —Xaa5—Xaa6—Xaa7—Z;
  Xaa1 is not present or is selected from the group consisting of amino acid residues Asn, Thr, Phe, 3- (2-thienyl) alanine (Thi), 4-chlorophenylalanine (Cpa) , α-

naphthylalanine (α-Nal) , β-naphthylalanine (β-Nal) , 1,2,3,4-tetrahydronorharman-3-carboxylic acid (Tpi), Tyr, 3-iodo-tyrosine (o-I-Tyr) , Trp and pentafluorophenylalanine (5-F-Phe) (all as L- or D-isomers) ;
Xaa2 is Gln, Asn or His;
Xaa3 is Trp or 1, 2, 3, 4-tetrahydronorharman-3-carboxylic acid (Tpi);
Xaa4 is Ala, Ser or Val;
Xaa5 is Val, Ser or Thr;
Xaa6 is Gly, sarcosine (Sar), D-Ala, or β-Ala;
Xaa7 is His or (3-methyl)histidine (3-Me)His;
Z is selected from -NHOH, -NHNH2, -NH-alkyl, -N(alkyl)2, and -O-alkyl
or Z is



wherein X is NH (amide) or O (ester) and R1 and R2 are the same or different and selected from a proton, an optionally substituted alkyl, an optionally substituted alkyl ether, an aryl, an aryl ether or an alkyl-, halogen, hydroxyl or hydroxyalkyl substituted aryl or heteroaryl group; and

- the radiolabeled GRPR-antagonist is administered to said subject at a therapeutically efficient amount comprised between 2000 and 10000 MBq.

In yet another aspect, the present disclosure refers to a method for in vivo imaging of tumors in a subject in need thereof, in particular for detecting GRPR positive tumors, the method comprising an effective amount of a composition as disclosed herein to be administered to said subject and detecting the signal derived from the decay of the radioisotope present in said compound, thereby detecting GRPR positive tumors.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

Figure 1A. Figure 1A shows SPECT/CT images 4 hours and 24 hours post the 1st injection, and 4 hours post the 2nd and 3rd injection. Arrows indicate the tumor. Animals were either injected with 30 MBq/300 pmol (group 1), 40 MBq/400 pmol (group 2) or 60 MBq/600 pmol ^{177}Lu-NeoBOMB1.

Figure 1B. Figure 1B shows quantified tumor uptake (n=2 per group) from the injections described in Figure 1A.

Figure 2A,B. Figure 2A shows extrapolated tumor size of untreated animals and animals treated with 3 × 30 MBq/300 pmol (group 1), 3 × 40 MBq/400 pmol (group 2) and 3 × 60 MBq/600 pmol ^{177}Lu-NeoBOMB1 (group 3). Figure 2B shows survival of untreated

CLAIMS

1. A pharmaceutical composition comprising

- a radiolabeled GRPR-antagonist of the following formula:

  MC- S - P

  wherein :

  M is a radiometal and C is a chelator which binds M;

  S is an optional spacer covalently linked between C and the N-terminal of P;

  P is a GRP receptor peptide antagonist of the general formula :

  Xaa1-Xaa2—Xaa3—Xaa4 —Xaa5—Xaa6—Xaa7—Z;

  Xaa1 is not present or is selected from the group consisting of amino acid residues Asn, Thr, Phe, 3- (2-thienyl) alanine (Thi), 4-chlorophenylalanine (Cpa) , α-naphthylalanine (α-Nal) , β-naphthylalanine (β-Nal) , 1,2,3,4-tetrahydronorharman-3-carboxylic acid (Tpi), Tyr, 3-iodo-tyrosine (o-I-Tyr) , Trp and pentafluorophenylalanine (5-F-Phe) (all as L- or D-isomers) ;

  Xaa2 is Gln, Asn or His;

  Xaa3 is Trp or 1, 2, 3, 4-tetrahydronorharman-3-carboxylic acid (Tpi);

  Xaa4 is Ala, Ser or Val;

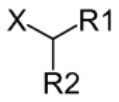
  Xaa5 is Val, Ser or Thr;

  Xaa6 is Gly, sarcosine (Sar), D-Ala, or β-Ala;

  Xaa7 is His or (3-methyl)histidine (3-Me)His;

  Z is selected from -NHOH, -NHNH2, -NH-alkyl, -N(alkyl)2, and -O-alkyl

  or Z is

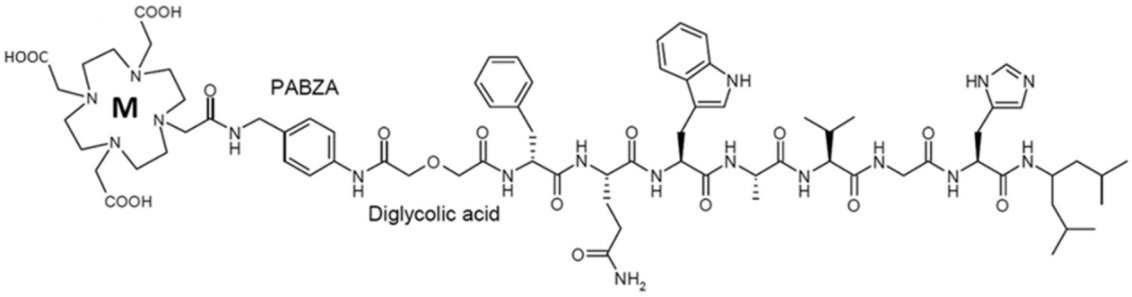
  

  wherein X is NH (amide) or O (ester) and R1 and R2 are the same or different and selected from a proton, an optionally substituted alkyl, an optionally substituted alkyl ether, an aryl, an aryl ether or an alkyl-, halogen, hydroxyl or hydroxyalkyl substituted aryl or heteroaryl group; and,

- a surfactant comprising a compound having (i) a polyethylene glycol chain and (ii) a fatty acid ester.

2. The pharmaceutical composition according to claim 1 wherein P is DPhe-Gln-Trp-Ala-Val-Gly-His-NH-CH(CH_2-CH(CH_3)$_2$)$_2$.

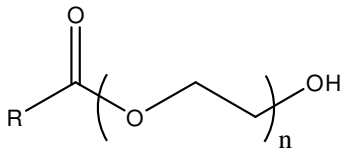
3. The pharmaceutical composition according to claim 1 or 2 wherein the GRPR-antagonist is NeoBOMB1 of formula (I):



(I)

wherein M is a radiometal, preferably M is selected from ^{177}Lu, ^{68}Ga.

4. The pharmaceutical composition according to any of the preceding claims wherein the surfactant comprises a compound of formula (III):



(III)

wherein n is comprised between 3 and 1000, preferably between 5 and 500, and more preferably between 10 and 50, and

R is the fatty acid chain, preferably an optionally substituted aliphatic chain.

5. The pharmaceutical composition according to any of the preceding claims wherein the surfactant comprises polyethylene glycol 15-hydroxystearate and free ethylene glycol.

6. The pharmaceutical composition according to any of the preceding claims, wherein the radiolabeled GRPR-antagonist is present in a concentration providing a volumetric radioactivity of at least at least 100 MBq/mL, preferably between 250 MBq/mL and 500 MBq/mL.

7. The pharmaceutical composition according to any of the preceding claims, wherein the surfactant is present in a concentration of at least 5 µg/mL, preferably at least 25 µg/mL, and between 50 µg/mL and 1000 µg/mL.

8. The pharmaceutical composition according to any of the preceding claims, wherein the radiolabeled GRPR-antagonist is labeled with ^{177}Lu, ^{68}Ga or ^{111}In.

9. The pharmaceutical composition according to any of the preceding claims wherein the pharmaceutical composition is an aqueous solution.

10. The pharmaceutical composition according to any of the preceding claims wherein the pharmaceutical composition is a solution for infusion.

11. The pharmaceutical composition according to any of claims 1 to 10, for use in treating or preventing cancer.

12. The pharmaceutical composition according to any of claims 1 to 10, for use in in vivo imaging, preferably PET and SPECT imaging.

13. Use of a composition according to any of claims 1 to 10 in the manufacture of a medicament for treating or preventing cancer.

14. A method for in vivo imaging of tumors in a subject in need thereof, in particular for detecting GRPR positive tumors, the method comprising an effective amount of a composition according to any of claims 1 to 10 to be administered to said subject and detecting the signal derived from the decay of the radioisotope present in said compound, thereby detecting GRPR positive tumors.