CLAIMS

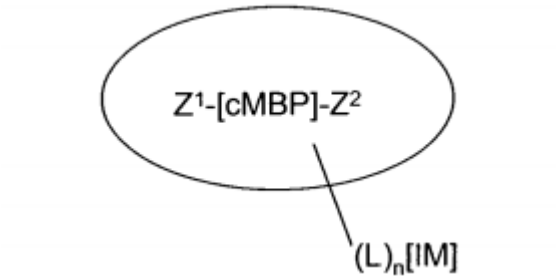
1. A lyophilised formulation comprising:

(i) an active pharmaceutical ingredient (API);

(ii) a buffering agent; and

(iii) a lyoprotectant;

wherein the API is an imaging agent comprising at least one cMet binding peptide, suitable for optically imaging the mammalian body, the imaging agent comprising a compound of Formula I:



(Formula I)

wherein:

Z^1 is attached to the N-terminus of cMBP, and is H or M^{IG};

Z^2 is attached to the C-terminus of cMBP, and is OH, NH_2, OB^c or M^{IG};

wherein B^c is a biocompatible cation;

cMBP is a cMet binding cyclic peptide of 17 to 30 amino acids, which comprises the amino acid sequence (SEQ-1):

Cys^a-Xaa^1-Cys^c-Xaa^2-Gly-Pro-Pro-Xaa^3-Phe-Glu-Cys^d-Trp-Cys^b-Tyr-Xaa^4-Xaa^5-Xaa^6;

wherein: Xaa^1 is Asn, His or Tyr;

Xaa^2 is Gly, Ser, Thr or Asn;

Xaa^3 is Thr or Arg;

Xaa^4 is Ala, Asp, Glu, Gly or Ser;

Xaa^5 is Ser or Thr;

Xaa^6 is Asp or Glu;

and Cys^{a-d} are each cysteine residues such that residues a and b as well as c and d are cyclised to form two separate disulphide bonds;

M^{IG} is a metabolism inhibiting group, which is a biocompatible group that inhibits or suppresses *in vivo* metabolism of the peptide;

L is a synthetic linker group of formula –(A)m- wherein each A is independently $-CR_2-$, -CR=CR-, -C≡C-, $-CR_2CO_2-$, $-CO_2CR_2-$, -NRCO-, -CONR-, -NR(C=O)NR-, -NR(C=S)NR-, $-SO_2NR-$, $-NRSO_2-$, CR_2OCR_2-, $-CR_2SCR_2-$, CR_2NRCR_2-, a C_{4-8} cycloheteroalkylene group, a C_{4-8} cycloalkylene group, a C_{5-12} arylene group, a C_{3-12} heteroarylene group, an amino acid, a sugar or a monodisperse polyethyleneglycol (PEG) building block;

each R is independently chosen from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxyalkyl or C_{1-4} hydroxyalkyl;

m is an integer of value 1 to 20;

n is an integer of value 0 or 1;

IM is an optical reporter imaging moiety suitable for imaging the mammalian body using light of violet to near-infrared wavelength (400 to 1,200 nm);

wherein the formulation comprises from 4 to 12 % by weight API, from 3 to 35 % by weight buffering agent, and from 56 to 91 % by weight lyoprotectant; and wherein the formulation, when reconstituted, has a pH of between pH 6.8 and pH 9.

2. The lyophilised formulation of claim 1, wherein in addition to SEQ-1, the cMBP further comprises an Asp or Glu residue, or an analogue thereof, within 4 amino acid residues of either C- or N- cMBP peptide terminus, and $–(L)_nIM$ is functionalised with an amine group, which is conjugated to the carboxyl side chain of said Asp or Glu residue, or analogue thereof, to give an amide bond.

3. The lyophilised formulation of claim 1 or claim 2, wherein in addition to SEQ-1, the cMBP comprises a Lys residue, or an analogue thereof, within 4 amino acid residues of either C- or N- cMBP peptide terminus, and $–(L)_nIM$ is functionalised with a carboxyl group, which is conjugated to the epsilon amine side chain of said Lys residue, or analogue thereof, to give an amide bond.

4. The lyophilised formulation of any one of claims 1 to 3, wherein cMBP comprises the amino acid sequence of either SEQ-2 or SEQ-3:
Ser-Cys^a-Xaa^1-Cys^c-Xaa^2-Gly-Pro-Pro-Xaa^3-Phe-Glu-Cys^d-Trp-Cys^b-Tyr-Xaa^4-Xaa^5-Xaa^6 (SEQ-2);

Ala-Gly-Ser-Cys^a-Xaa^1-Cys^c-Xaa^2-Gly-Pro-Pro-Xaa^3-Phe-Glu-Cys^d-Trp-Cys^b-Tyr-Xaa^4-Xaa^5-Xaa^6-Gly-Thr (SEQ-3).

5. The lyophilised formulation of any preceding claim, wherein Xaa^3 is Arg.

6. The lyophilised formulation of any preceding claim, wherein in addition to SEQ-1, SEQ-2 or SEQ-3, cMBP further comprises at either the N- or C- terminus a linker peptide, which is chosen from -Gly-Gly-Gly-Lys (SEQ-4), -Gly-Ser-Gly-Lys- (SEQ-5) and -Gly-Ser-Gly-Ser-Lys (SEQ-6).

7. The lyophilised formulation of any preceding claim, wherein cMBP comprises the amino acid sequence (SEQ-7):
Ala-Gly-Ser-Cys[a]-Tyr-Cys[c]-Ser-Gly-Pro-Pro-Arg-Phe-Glu-Cys[d]-Trp-Cys[b]-Tyr-Glu-Thr-Glu-Gly-Thr-Gly-Gly-Gly-Lys.

8. The lyophilised formulation of any preceding claim, wherein both Z^1 and Z^2 are independently M^{IG}.

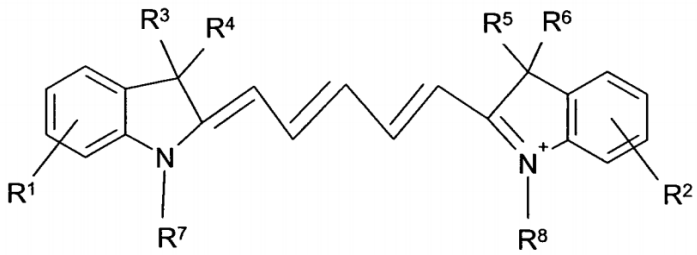
9. The lyophilised formulation of any preceding claim, wherein Z^1 is acetyl and Z^2 is a primary amide.

10. The lyophilised formulation of any preceding claim, wherein n is 0.

11. The lyophilised formulation of any preceding claim, wherein IM is a dye having an absorbance maximum in the range 600 to 1,000 nm.

12. The lyophilised formulation of claim 11, wherein IM is a cyanine dye.

13. The lyophilised formulation of claim 12, wherein the cyanine dye has Formula III:



(Formula III)

wherein:

R^1 and R^2 are independently H or SO_3M^1, and at least one of R^1 and R^2 is SO_3M^1, where M^1 is H or B^c;

R^3 and R^4 are independently C_{1-4} alkyl or C_{1-6} carboxyalkyl;

R^5, R^6, R^7 and R^8 are independently R^a groups;

wherein R^a is C_{1-4} alkyl, C_{1-6} carboxyalkyl or $–(CH_2)_kSO_3M^1$, where k is an integer of value 3 or 4;

with the proviso that the cyanine dye has a total of 1 to 4 SO_3M^1 substituents in the R^1, R^2 and R^a groups.

14. The lyophilised formulation of any preceding claim, wherein the formulation, when reconstituted, has a pH of between pH 6.5 and pH 8.5, optionally between pH 6.8 and pH 8.2, optionally between pH 6.8 and pH 8, optionally between pH 7 and pH 8.

15. The lyophilised formulation of any preceding claim, wherein the buffering agent is present in an amount to provide, when reconstituted, a solution having a pH of between pH 6.3 and pH 9, optionally between pH 6.3 and pH 9, optionally between pH 6.5 and pH 8.5, optionally between pH 6.8 and pH 8.2, optionally between pH 6.8 and pH 8, optionally between pH 7 and pH 8.

16. The lyophilised formulation of any preceding claim, wherein the mole ratio of the API : buffering agent is 1 mole of API : 17 to 47 moles of buffering agent, optionally 1 mole of API : 27 to 47 moles of buffering agent, optionally 1 mole of API : 30 to 47 moles of buffering agent, optionally 1 mole of API : 34 to 47 moles of buffering agent, optionally 1 mole of API : 27 to 38 moles of buffering agent, optionally 1 mole of API : 30 to 38 moles of buffering agent, optionally 1 mole of API : 34 to 38 moles of buffering agent.

17. The lyophilised formulation of any preceding claim, wherein the mole ratio of API : lyoprotectant is 1 mole API : 105 to 216 moles of lyoprotectant, optionally 1 mole API : 105 to 163 moles of lyoprotectant, optionally 1 mole API : 105 to 154 moles of lyoprotectant, optionally 1 mole API : 105 to 145 moles of lyoprotectant, optionally 1 mole API : 105 to 141 moles of lyoprotectant, optionally 1 mole API : 105 to 132 moles of lyoprotectant, optionally 1 mole API : 105 to 129 moles of lyoprotectant, optionally 1 mole API : 129 to 216 moles of lyoprotectant, optionally 1 mole API : 129 to 163 moles of lyoprotectant, optionally 1 mole API : 129 to 154 moles of lyoprotectant, optionally 1 mole API : 129 to 145 moles of lyoprotectant, optionally 1 mole API : 129 to 141 moles of lyoprotectant, optionally 1 mole API : 129 to 132 moles of lyoprotectant.

18. The lyophilised formulation of any preceding claim, wherein the formulation comprises from 8 to 10 % by weight API, optionally 9 % by weight API.

19. The lyophilised formulation of any preceding claim, wherein the formulation comprises from 7 to 35 % by weight buffering agent, optionally from 12 to 35 % by weight buffering agent, optionally from 15 to 35 % by weight buffering agent, optionally from 18 to 35 % by weight buffering agent, optionally from 25 to 35 % by weight buffering agent, optionally from 32 to 35 % by weight buffering agent, optionally 32 % by weight buffering agent.

20. The lyophilised formulation of any preceding claim, wherein the formulation comprises from 56 to 82 % by weight lyoprotectant,

optionally from 56 to 77 % by weight lyoprotectant, optionally from 56 to 75 % by weight lyoprotectant, optionally from 56 to 72 % by weight lyoprotectant, optionally from 56 to 66 % by weight lyoprotectant, optionally from 56 to 58 % by weight lyoprotectant, optionally 58 % by weight lyoprotectant.

21. The lyophilised formulation of any preceding claim, wherein the buffering agent is at least one of a phosphate buffer and an alkanolamine buffer.

22. The lyophilised formulation of claim 21, wherein the phosphate buffer comprises hydrogen phosphate and dihydrogen phosphate, optionally wherein the phosphate buffer is hydrated.

23. The lyophilised formulation of claim 21 or claim 22, wherein the alkanolamine buffer is tris(hydroxymethyl)aminomethane.

24. The lyophilised formulation of any preceding claim, wherein the lyoprotectant is at least one of sucrose and mannitol, and derivatives thereof.

25. The lyophilised formulation of any preceding claim, wherein the lyoprotectant is mannitol, or a derivative thereof.

26. The lyophilised formulation of any preceding claim, wherein the formulation further comprises a tonicity regulator.

27. The lyophilised formulation of any preceding claim, wherein the lyoprotectant also acts as a tonicity regulator.

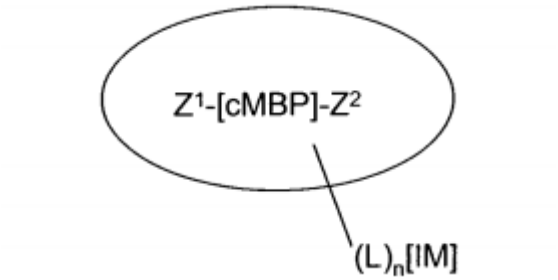
28. A method of preparing a lyophilised formulation, the method comprising the steps of:

a) providing an active pharmaceutical ingredient (API), a buffering agent, and a lyoprotectant to a lyophilisation vessel;

b) performing a first water removal step; and

c) performing a second water removal step;

wherein the lyoprotectant and the buffering agent are added before the lyophilisation is carried out, and the API is an imaging agent comprising at least one cMet binding peptide, suitable for optically imaging the mammalian body, the imaging agent comprising a compound of Formula I:



(Formula I)

wherein:

Z^1 is attached to the N-terminus of cMBP, and is H or M^{IG};

Z^2 is attached to the C-terminus of cMBP, and is OH, NH_2, OB^c or M^{IG};

wherein B^c is a biocompatible cation;

cMBP is a cMet binding cyclic peptide of 17 to 30 amino acids, which comprises the amino acid sequence (SEQ-1):

Cys^a-Xaa^1-Cys^c-Xaa^2-Gly-Pro-Pro-Xaa^3-Phe-Glu-Cys^d-Trp-Cys^b-Tyr-Xaa^4-Xaa^5-Xaa^6;

wherein: Xaa^1 is Asn, His or Tyr;

Xaa^2 is Gly, Ser, Thr or Asn;

Xaa^3 is Thr or Arg;

Xaa^4 is Ala, Asp, Glu, Gly or Ser;

Xaa^5 is Ser or Thr;

Xaa^6 is Asp or Glu;

and Cys^{a-d} are each cysteine residues such that residues a and b as well as c and d are cyclised to form two separate disulphide bonds;

M^{IG} is a metabolism inhibiting group, which is a biocompatible group that inhibits or suppresses *in vivo* metabolism of the peptide;

L is a synthetic linker group of formula –(A)m- wherein each A is independently $-CR_2-$, -CR=CR-, -C≡C-, $-CR_2CO_2-$, $-CO_2CR_2-$, -NRCO-, -CONR-, -NR(C=O)NR-, -NR(C=S)NR-, $-SO_2NR-$, $-NRSO_2-$, CR_2OCR_2-, $-CR_2SCR_2-$, CR_2NRCR_2-, a C_{4-8} cycloheteroalkylene group, a C_{4-8} cycloalkylene group, a C_{5-12} arylene group, a C_{3-12} heteroarylene group, an amino acid, a sugar or a monodisperse polyethyleneglycol (PEG) building block;

each R is independently chosen from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxyalkyl or C_{1-4} hydroxyalkyl;

m is an integer of value 1 to 20;

n is an integer of value 0 or 1;

IM is an optical reporter imaging moiety suitable for imaging the mammalian body using light of violet to near-infrared wavelength (400 to 1,200 nm);

wherein the formulation comprises from 4 to 12 % by weight API, from 3 to 35 % by weight buffering agent, and from 56 to 91 % by weight lyoprotectant; and wherein the formulation, when reconstituted, has a pH of between pH 6.8 and pH 9.

29. The method of claim 28, wherein the first water removal step is carried out at a temperature of -30 °C or lower, optionally -35 °C or lower, optionally -38 °C or lower.

30. The method of claim 28 or claim 29, wherein the second water removal step is carried out at a temperature of 10 °C or higher, optionally 15 °C or higher, optionally 20 °C or higher.

31. The method of any one of claims 28 to 30, wherein at least one of the first and second water removal steps is carried out at a pressure of 50 µbar or less.

32. The method of any one of claims 28 to 31, wherein both of the first and second water removal steps are carried out at a pressure of 50 µbar or less.

33. The method of any one of claims 28 to 32, wherein the lyophilised formulation is the lyophilised formulation any one of claim 1 to 27.

34. A pharmaceutical composition comprising the formulation of any one of claims 1 to 27 and a biocompatible carrier, in a form suitable for mammalian administration.

35. The pharmaceutical composition of claim 34, wherein the pharmaceutical composition has a pH of between pH 6.5 and pH 8.5, optionally between pH 6.8 and pH 8.2, optionally between pH 7 and pH 8.

36. A kit for the preparation of the pharmaceutical composition of claim 34 or claim 35, the kit comprising the formulation of any one of claim 1 to 27 in sterile, solid form such that upon reconstitution with a sterile supply of the biocompatible carrier of claim 34 or claim 35, dissolution occurs to give the desired pharmaceutical composition.

37. A method of imaging of the mammalian body comprising use of at least one of the formulation of any one of claim 1 to 27 and the pharmaceutical composition of claim 34 or claim 35.

38. The method of claim 37, wherein the imaging is *in vivo*.

39. The method of claim 37 or claim 38, wherein the imaging is optical imaging.

40. The method of any one of claims 37 to 39, wherein the imaging is to obtain images of sites of cMet over-expression or localisation.

41. The method of any one of claims 37 to 40, wherein the formulation of any one of claim 1 to 27 or the pharmaceutical composition of claim 34 or claim 35 has been previously administered to the mammalian body.

42. The method of any one of claims 37 to 41, wherein the method comprises the steps of:

a) illuminating a tissue surface of interest with an excitation light;
b) detecting fluorescence from the imaging agent, which is generated by excitation of the imaging agent;
c) optionally filtering the light detected by the fluorescence detector to separate out the fluorescent component; and

d) forming an image of the tissue surface of interest from the fluorescent light of steps (b) or (c).

43. The method of claim 42, wherein the excitation light of step (a) is continuous wave (CW) in nature.

44. The method of any one of claims 37 to 41, wherein the method comprises the steps of:

a) exposing light-scattering biologic tissue of said mammalian body having a heterogeneous composition to light from a light source with a pre-determined time varying intensity to excite the imaging agent, the tissue multiply-scattering the excitation light;

b) detecting a multiply-scattered light emission from the tissue in response to said exposing;

c) quantifying a fluorescence characteristic throughout the tissue from the emission by establishing a number of values with a processor, the values each corresponding to a level of the fluorescence characteristic at a different position within the tissue, the level of the fluorescence characteristic varying with heterogeneous composition of the tissue; and

d) generating an image of the tissue by mapping the heterogeneous composition of the tissue in accordance with the values of step (c).

45. The method of any one of claims 37 to 44, wherein the optical imaging method comprises fluorescence imaging, optionally fluorescence endoscopy.

46. The method of any one of claims 37 to 45, wherein the method is used to assist in detection, diagnosis, surgery, staging, treatment,

monitoring of treatment, monitoring of disease progression or monitoring therapy.

47. The method of any one of claims 37 to 46, wherein the method is used to assist in detection, diagnosis, surgery, staging, treatment, monitoring of treatment, monitoring of disease progression or monitoring therapy of one or more of a precancerous condition and cancer, optionally one or more of colorectal cancer, oesophageal cancer, breast cancer, prostate cancer, head cancer, neck cancer, ovarian cancer, rectal cancer, pancreatic cancer, thyroid cancer, gastric cancer and sarcoma.

48. The formulation of any one of claims 1 to 27, or the pharmaceutical composition of claim 34 or claim 35, for use as an imaging agent in imaging of the mammalian body.

49. The formulation of any one of claims 1 to 27, or the pharmaceutical composition of claim 34 or claim 35, for use in detection, , , staging, , monitoring of treatment, monitoring of disease progression or monitoring therapy.

50. The formulation of any one of claims 1 to 27, or the pharmaceutical composition of claim 34 or claim 35, for use in the detection, , , staging, , monitoring of treatment, monitoring of disease progression or monitoring therapy of one or more of a precancerous condition and cancer, optionally one or more of colorectal cancer, oesophageal cancer, breast cancer, prostate cancer, head cancer, neck cancer, ovarian cancer, rectal cancer, pancreatic cancer, thyroid cancer, gastric cancer and sarcoma.

51. The formulation of any one of claims 1 to 27, or the pharmaceutical composition of claim 34 or claim 35, for use in the detection, , , staging, , monitoring of treatment, monitoring of disease progression or monitoring therapy of sites of cMet over-expression or localisation.

52. The formulation of any one of claims 1 to 27, or the pharmaceutical composition of claim 34 or claim 35, for use in obtaining an image of sites of cMet over-expression or localisation, optionally *in vivo*.

53. A method of obtaining an image of sites of cMet over-expression or localisation, optionally *in vivo,* using at least one of the formulation of any one of claims 1 to 27, and the pharmaceutical composition of claim 34 or claim 35.

54. The use of at least one of the formulation of any one of claims 1 to 27, and the pharmaceutical composition of claim 34 or claim 35, as an imaging agent.

55. The use of at least one of the formulation of any one of claims 1 to 27, and the pharmaceutical composition of claim 34 or claim 35, in obtaining an image of sites of cMet over-expression or localisation, optionally *in vivo*.