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Datasheet for the decision of 1 October 2008

Case Number: T 0867/02 - 3.3.02

Application Number: 93915221.1

Publication Number: 0644778

IPC: A61K 51/00

Language of the proceedings: EN

Title of invention:
Technetium-99m labeled peptides for imaging

Patentee:
CIS bio international

Opponent:
Bristol-Myers Squibb Pharma Company

Headword:
Reagents for scintigraphic imaging/CIS BIO INTERNATIONAL

Relevant legal provisions:
EPC Art. 54, 56, 84, 123(2), 123(3), 52(4), 111(1)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request and auxiliary requests 1-4 - novelty - (no)"
"Auxiliary requests 5 and 6 - admissibility - (no): late filed and not caused by new facts or arguments"
"Auxiliary request 6a - novelty and inventive step - (yes): introduction of branching units into the molecules not obvious"
"Remittal - (yes): adaptation of the description"

Decisions cited:
-

Catchword:
-

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Case Number: T 0867/02 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 1 October 2008

Appellant: (Opponent)	Bristol-Meyers Squibb Pharma Company 203 Longmeadow Drive Wilmington DE19810 (US)
Representative:	Warner, James Alexander Carpmaels and Ransford 43 Bloomsbury Square London WC1A 2RA (GB)
Appellant: (Patent Proprietor)	CIS bio international RN 306 Saclay B.P. 32 F-91192 Gif sur Yvette Cedex (FR)
Respondent:	Eder, Michael Dörries Frank-Molnia Pohlman Postfach 22 16 61 D-80506 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 18 June 2002 concerning maintenance of European patent No. 0644778 in amended form.**

Composition of the Board:

Chairman: J. Riolo
Members: A. Lindner
P. Mühlens

Summary of Facts and Submissions

I. European patent No. 0 644 778 based on application No. 93 915 221.1 was granted on the basis of a set of 17 claims.

The independent claims read as follows:

" 1. A reagent for preparing a scintigraphic imaging agent for imaging sites within a mammalian body comprising a multiplicity of specific-binding peptide moieties, each specific binding peptide having an amino acid sequence of 3 to 100 amino acids, covalently linked to a polyvalent linking moiety, and a technetium-99m binding moiety covalently linked to a plurality of the specific-binding peptides, the polyvalent linker moiety, or both, said reagent optionally being radiolabeled with technetium-99m.

10. A complex formed by reacting a reagent of any one of claims 1 to 9 with technetium-99m in the presence of a reducing agent, optionally dithionite ion, stannous ion or ferrous ion, or by labeling said reagent with technetium-99m by ligand exchange of a prereduced technetium-99m complex.

11. A kit for preparing a radiopharmaceutical preparation, predetermined quantity of a reagent of any one of claims 1 to 9 and a sufficient amount of reducing agent to label the reagent with technetium-99m.

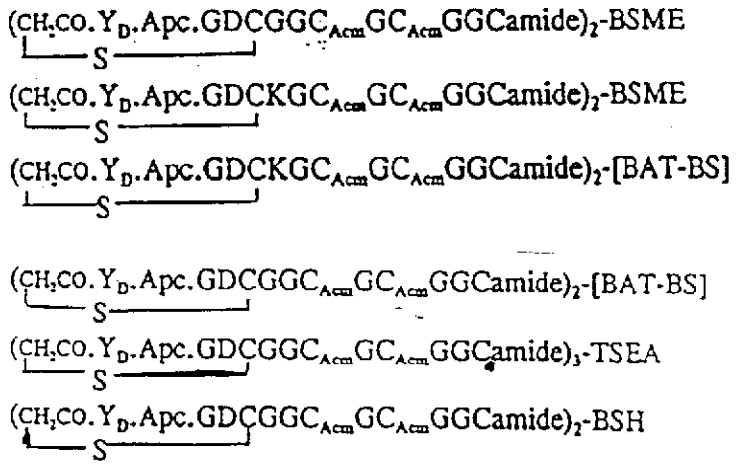
12. A method for labeling a reagent according to any one of claims 1 to 9 comprising reacting the reagent with

technetium-99m in the presence of a reducing agent, optionally dithionite ion, stannous ion or ferrous ion.

13. The use of a reagent of any one of claims 1 to 9 for the manufacture of a medicament for imaging a site within a mammalian body.

14. A reagent having a formula selected from the following, and optionally radiolabeled with technetium-99m:

(*acetyl*.F_DPRPG)$_2$KGGGCamide
(GPRVVERHQSA)$_2$K$C_{Acm}GC_{Acm}$amide
[(GPRP)$_2$K]$_2$K$C_{Acm}GC_{Acm}$amide



(*acetyl*.$CC_{Acm}GC_{Acm}$PLYKKIIKKLLES)$_2$-BSME
(*acetyl*.$CC_{Acm}GC_{Acm}$GGPLYKKIIKKLLES)$_2$-BSME
(*formyl*.MLFK(N_ε-BAT)GG$C_{Acm}GC_{Acm}$GGC.amide)$_2$-BSME
($CC_{Acm}GC_{Acm}$GGRGDS)$_3$-TSEA
(GPRP$C_{Acm}GC_{Acm}$Camide)$_3$-TSEA
(GPRPPPGG$C_{Acm}GC_{Acm}$GGCamide)$_3$-TSEA
(Pic.SC_{Acm}SYNRGDSTCamide)$_3$-TSEA
(RALVDTLKGG$C_{Acm}GC_{Acm}$Camide)$_3$-TSEA
(*ma*.GGGRALVDTLKFVTQAEGAKamide)$_2$-[BAT-BS]
(GRGDF$C_{Acm}GC_{Acm}$Camide)$_3$-TSEA
(Pic.GC_{Acm}RALVDTLKFVTQAEGAKCamide)$_3$-TSEA

(*acetyl*.SYNRGDT$C_{Acm}GC_{Acm}$Camide)$_3$-DMAB .

15. An article comprising a sealed vial containing a predetermined quantity of a reagent of claim 14 and a sufficient amount of reducing agent to label the composition with technetium-99m.

16. A pharmaceutical composition comprising a diagnostically-effective amount of a reagent as defined in any one of claims 1 to 9 and a pharmaceutically acceptable carrier.

17. The use of a reagent according to any one of claims 1 to 4 as a scintigraphic imaging agent for imaging a site within the mammalian body."

II. An opposition was filed against the granted patent by the Du Pont Merck Pharmaceutical Company. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step and for non-compliance with the requirements of Article 52(4) EPC and under Article 100(c) EPC because its subject-matter extended beyond the content of the application as filed.

III. The following documents were *inter alia* cited during the opposition and appeal proceedings:

(1) WO 90/03798

(2) The British Journal of Radiology, 65 (1992), 112-118

(3) Proc. Natl. Acad. Sci. USA, vol. 85 (1988), 4025-4029

(4) Cancer Research (suppl.) 50 (1990), 799s-803s

(5) WO 88/01178

(6) WO 93/12819

(9) WO 93/23085

(16) Priority document of document (9)

IV. In the decision pronounced on 13 March 2002, the opposition division maintained the patent in amended form on the basis of auxiliary request 3 filed at the

oral proceedings. The main request was rejected for non-compliance with the requirements of Article 123(2) EPC. As for claim 1 of auxiliary requests 1 and 2, the opposition division came to the conclusion that the subject-matter claimed therein lacked novelty over documents (1) and (9). As regards auxiliary request 3, the principal findings of the opposition division were as follows:

The subject-matter as claimed was clear, as the abbreviations used in claims 1 and 14 were explained in the description. Moreover, novelty was acknowledged, as the combination of features of claim 1 was neither disclosed in document (1) nor in document (9). With regard to inventive step, document (1) was defined as closest prior art. The person skilled in the art, trying to replace DTPA by a more efficient ^{99m}Tc binding moiety would not combine the teaching of document (1) with the teaching of document (3) or (4) in view of the considerable structural differences between proteins (documents (3) and (4)) and peptides (document (1)). As a consequence, an inventive step for auxiliary request 3 was acknowledged.

V. Both the patentee and the opponent lodged an appeal against that decision.

VI. First oral proceedings were held on 20 June 2007. During the discussion, the board indicated that the feature "specific binding moiety" did not appear to imply any structural restriction for the peptide so that the relevance of the state of the art would have to be interpreted differently. In view of the fact that this interpretation of the claimed subject-matter was

mentioned for the first time, the appellant-patentee requested that the proceedings be continued in writing, to which request the appellant-opponent did not raise any objections.

VII. Second oral proceedings were held on 1 October 2008. The following independent claims are relevant for this decision:

(a) main request:

" 1. A reagent for preparing a scintigraphic imaging agent for imaging sites within a mammalian body comprising a multiplicity of specific-binding peptide moieties, each specific-binding peptide having an amino acid sequence of 3 to 100 amino acids, covalently linked to a polyvalent linking moiety, and a technetium-99m binding moiety covalently linked to a plurality of the specific-binding peptides, the polyvalent linker moiety, or both, said reagent optionally being radiolabeled with technetium-99m,

with the proviso that the reagent is neither of the following structures:

$[Pic.SC_{Acm}SYNRGDSTC.amide]_3$-TSEA;
$(GPRPC_{Acm}GC_{Acm}C.amide)_3$-TSEA
$[(GPRP)_2K]_2KC_{Acm}GC_{Acm}$amide;
$C_{Acm}GC_{Acm}$GGRGDGGRGDS;
$C_{Acm}GC_{Acm}$GGRGDGGRGDGGRGDS;
$GRGDVRGDFKC_{Acm}GC_{Acm}$.amide; and
$GRGDVRGDFC_{Acm}GC_{Acm}$.amide."

(b) auxiliary request 1:

" 1. A reagent for preparing a scintigraphic imaging agent for imaging sites within a mammalian body comprising a multiplicity of specific-binding peptide moieties, each specific-binding peptide having an amino acid sequence of 3 to 100 amino acids, covalently linked to a polyvalent linking moiety, and a technetium-99m binding moiety covalently linked to a plurality of the specific-binding peptides, the polyvalent linker moiety, or both, said reagent optionally being radiolabeled with technetium-99m, wherein said specific binding peptide accumulates at an organ, a tumor, a thrombus site or a site of infection;

with the proviso that the reagent is neither of the following structures:
$[Pic.SC_{Acm}SYNRGDSTC.amide]_3$-TSEA;
$(GPRPC_{Acm}GC_{Acm}C.amide)_3$-TSEA
$[(GPRP)_2K]_2KC_{Acm}GC_{Acm}amide$;
$C_{Acm}GC_{Acm}GGRGDGGRGDS$;
$C_{Acm}GC_{Acm}GGRGDGGRGDGGRGDS$;
$GRGDVRGDFKC_{Acm}GC_{Acm}.amide$; and
$GRGDVRGDFC_{Acm}GC_{Acm}.amide$."

(c) auxiliary request 2:

" 1. Use of a reagent for preparing a scintigraphic imaging agent for imaging sites within a mammalian body, wherein said reagent comprises a multiplicity of specific-binding peptide moieties, each specific-binding peptide having an amino acid sequence of 3 to 100 amino acids, covalently linked to a polyvalent linking moiety, and a technetium-99m binding moiety covalently linked to

a plurality of the specific-binding peptides, the polyvalent linker moiety, or both, said reagent optionally being radiolabeled with technetium-99m,

with the proviso that the reagent is neither of the following structures:

$[Pic.SC_{Acm}SYNRGDSTC.amide]_3$-TSEA;
$(GPRPC_{Acm}GC_{Acm}C.amide)_3$-TSEA
$[(GPRP)_2K]_2KC_{Acm}GC_{Acm}amide$;
$C_{Acm}GC_{Acm}GGRGDGGRGDS$;
$C_{Acm}GC_{Acm}GGRGDGGRGDGGRGDS$;
$GRGDVRGDFKC_{Acm}GC_{Acm}.amide$; and
$GRGDVRGDFC_{Acm}GC_{Acm}.amide$."

(d) auxiliary request 3:

" 1. A kit for preparing a radiopharmaceutical preparation containing a predetermined quantity of a reagent for preparing a scintigraphic imaging agent for imaging sites within a mammalian body and a sufficient amount of a reducing agent to label the reagent with technetium-99m, wherein said reagent comprises a multiplicity of specific-binding peptide moieties, each specific-binding peptide having an amino acid sequence of 3 to 100 amino acids, covalently linked to a polyvalent linking moiety, and a technetium-99m binding moiety covalently linked to a plurality of the specific-binding peptides, the polyvalent linker moiety, or both, said reagent optionally being radiolabeled with technetium-99m,

with the proviso that the reagent is neither of the following structures:

$[Pic.SC_{Acm}SYNRGDSTC.amide]_3$-TSEA;
$(GPRPC_{Acm}GC_{Acm}C.amide)_3$-TSEA
$[(GPRP)_2K]_2KC_{Acm}GC_{Acm}$amide;
$C_{Acm}GC_{Acm}$GGRGDGGRGDS;
$C_{Acm}GC_{Acm}$GGRGDGGRGDGGRGDS;
GRGDVRGDFK$C_{Acm}GC_{Acm}$.amide; and
GRGDVRGDF$C_{Acm}GC_{Acm}$.amide."

(e) auxiliary request 4:

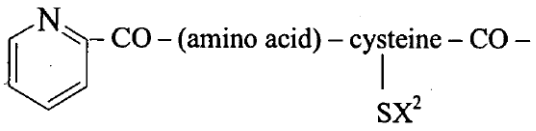
" 1. A reagent for preparing a scintigraphic imaging agent for imaging sites within a mammalian body comprising a multiplicity of specific-binding peptide moieties, each specific-binding peptide having an amino acid sequence of 3 to 100 amino acids, covalently linked to a polyvalent linking moiety, and a technetium-99m binding moiety covalently linked to a plurality of the specific-binding peptides, the polyvalent linker moiety, or both, said reagent optionally being radiolabeled with technetium-99m, wherein the technetium-99m binding moiety is selected from:

I.

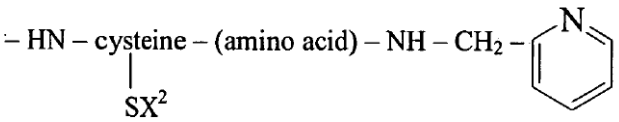
$C(pgp)^s$-(aa)-$C(pgp)^s$

wherein $C(pgp)^s$ is a cysteine having a protected thiol group and (aa) is an amino acid;

II.



III.



wherein

X^2 = H or a protecting group;

(amino acid) = any amino acid;

with the proviso that the reagent is neither of the following structures:

[Pic.SC_{Acm}SYNRGDSTC.amide]$_3$-TSEA;

(GPRP$C_{Acm}GC_{Acm}$C.amide)$_3$-TSEA

[(GPRP)$_2$K]$_2$K$C_{Acm}GC_{Acm}$amide;

$C_{Acm}GC_{Acm}$GGRGDGGRGDS;

$C_{Acm}GC_{Acm}$GGRGDGGRGDGGRGDS;

GRGDVRGDFK$C_{Acm}GC_{Acm}$.amide; and

GRGDVRGDF$C_{Acm}GC_{Acm}$.amide."

(f) auxiliary request 5:

Claim 1 of auxiliary request 5 is identical with claim 1 of auxiliary request 4 except that the following disclaimer was added at the end:

"…and further wherein the specific binding moiety does not specifically bind to a thrombus in vivo."

(g) auxiliary request 6:

" 1. A reagent for preparing a scintigraphic imaging agent for imaging sites within a mammalian body comprising a multiplicity of specific-binding peptide moieties, each specific-binding peptide having an amino acid sequence of 3 to 100 amino acids, covalently linked to a polyvalent linking moiety, and a technetium-99m binding moiety covalently linked to a plurality of the specific-binding peptides, the polyvalent linker moiety, or both, said reagent optionally being radiolabeled with technetium-99m, wherein the technetium-99m binding moiety is selected from:

I.

$C(pgp)^s$-(aa)-$C(pgp)^s$

wherein $C(pgp)^s$ is a cysteine having a protected thiol group and (aa) is an amino acid;

II.

A^1-$CZ^1(B^1)$-$[C(R^1R^2)]_n$-X^1

wherein

A^1 is H, HOOC, H_2NOC, or -NHOC

B^1 is SH or NHR^3

X^1 is H, methyl, SH or NHR^3

Z^1 is H or methyl;

R^1 and R^2 are independently H or lower alkyl;

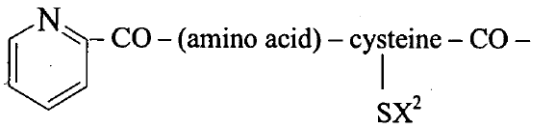
R^3 is H, lower alkyl or —C=O;

n is O, 1 or 2;

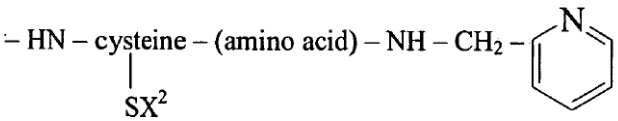
and where B^1 is NHR^3, X^1 is SH, Z^1 is H and n is 1 or 2; where X^1 is NHR^3, B^1 is SH, Z^1 is H and n is 1 or 2;

where B^1 is H, A^1 is HOOC, H_2NOC, or —NHOC, X^1 is SH, Z^1 is H and n is 0 or 1;
where Z^1 is methyl, X^1 is methyl, A^1 is HOOC, H_2NOC, or -NHOC, B^1 is SH and n is 0;
and wherein the thiol moiety is in the reduced form;

III.



IV.

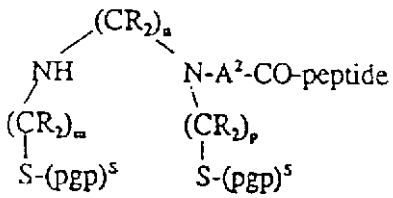


wherein

X^2 = H or a protecting group;

(amino acid) = any amino acid;

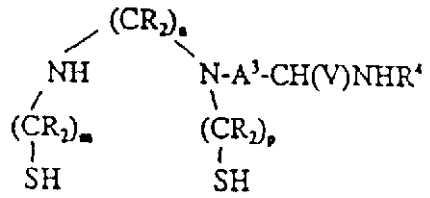
V.



wherein each R is independently H, CH_3 or C_2H_5;
each $(pgp)^s$ is independently a thiol protecting group or H;

m, n and p are independently 2 or 3;
A^2 = linear or cyclic lower alkyl, aryl, heterocyclyl, combinations or substituted derivatives thereof; and

VI.



wherein each R is independently H, CH_3 or C_2H_5;
m, n and p are independently 2 or 3;
A^3 = linear or cyclic lower alkyl, aryl, heterocyclyl, combinations or substituted derivatives thereof;
V = H or -CO-peptide;
R^4 = H or peptide; and wherein when V = H, R^4 = peptide and when R^4 = H, V = -CO-peptide; wherein each R is independently H, lower alkyl having 1 to 6 carbon atoms, phenyl, or phenyl substituted with lower alkyl or lower alkoxy, and wherein each n is independently 1 or 2;

and further wherein the polyvalent linking moiety is either a polyvalent linking moiety wherein a multiplicity of polyvalent linking moieties are covalently linked to form a branched polyvalent linking moiety; or
is selected from *bis*-succinimidylmethylether, 4-(2,2-dimethylacetyl)benzoic acid, N-[2-(N',N'bis(2-succinimidoethyl)aminoethyl)]-N^6,N^9-bis(2-methyl-2-mercaptopropyl)-6,9-diazanonanamide, *tris*(succinimidylethyl)amine, *bis*-succinimido-hexane, 4-(O-CH_2CO-Gly-Gly-Cys.amide)acetophenone or a derivative thereof;

with the proviso that the reagent is neither of the following structures:
$[Pic.SC_{Acm}SYNRGDSTC.amide]_3$-TSEA;
$(GPRPC_{Acm}GC_{Acm}C.amide)_3$-TSEA
$[(GPRP)_2K]_2KC_{Acm}GC_{Acm}$amide;"

(h) auxiliary request 6a:

" 1. A reagent for preparing a scintigraphic imaging agent for imaging sites within a mammalian body comprising a multiplicity of specific-binding peptide moieties, each specific-binding peptide having an amino acid sequence of 3 to 100 amino acids, covalently linked to a polyvalent linking moiety, and a technetium-99m binding moiety covalently linked to a plurality of the specific-binding peptides, the polyvalent linker moiety, or both, said reagent optionally being radiolabeled with technetium-99m, wherein the technetium-99m binding moiety is selected from:

I.

$$C(pgp)^s\text{-}(aa)\text{-}C(pgp)^s$$

wherein $C(pgp)^s$ is a cysteine having a protected thiol group and (aa) is an amino acid;

II.

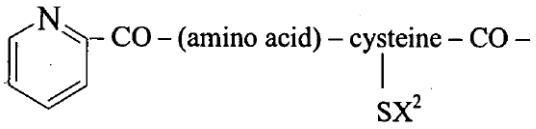
$$A^1\text{-}CZ^1(B^1)\text{-}[C(R^1R^2)]_n\text{-}X^1$$

wherein
A^1 is H, HOOC, H_2NOC, or -NHOC
B^1 is SH or NHR^3
X^1 is H, methyl, SH or NHR^3

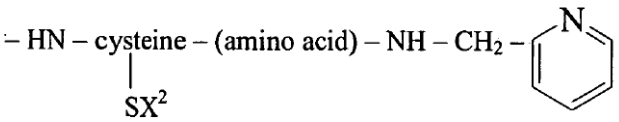
Z^1 is H or methyl;
R^1 and R^2 are independently H or lower alkyl;
R^3 is H, lower alkyl or –C=O;
n is O, 1 or 2;

and where B^1 is NHR^3, X^1 is SH, Z^1 is H and n is 1 or 2;
where X^1 is NHR^3, B^1 is SH, Z^1 is H and n is 1 or 2;
where B^1 is H, A^1 is HOOC, H_2NOC, or –NHOC, X^1 is SH, Z^1 is H and n is 0 or 1;
where Z^1 is methyl, X^1 is methyl, A^1 is HOOC, H_2NOC, or -NHOC, B^1 is SH and n is 0;
and wherein the thiol moiety is in the reduced form;

III.



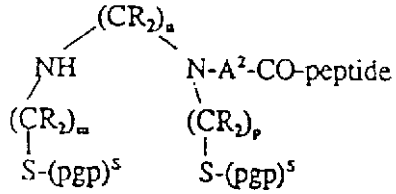
IV.



wherein

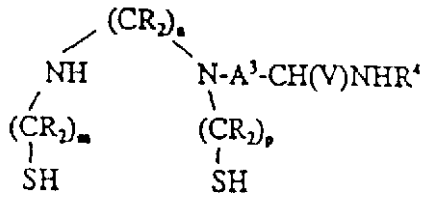
X^2 = H or a protecting group;
(amino acid) = any amino acid;

V.



wherein each R is independently H, CH_3 or C_2H_5;
each $(pgp)^s$ is independently a thiol protecting group or H;
m, n and p are independently 2 or 3;
A^2 = linear or cyclic lower alkyl, aryl, heterocyclyl, combinations or substituted derivatives thereof; and

VI.



wherein each R is independently H, CH_3 or C_2H_5;
m, n and p are independently 2 or 3;
A^3 = linear or cyclic lower alkyl, aryl, heterocyclyl, combinations or substituted derivatives thereof;
V = H or -CO-peptide;
R4 = H or peptide; and wherein when V = H, R^4 = peptide and when R^4 = H, V = -CO-peptide; wherein each R is independently H, lower alkyl having 1 to 6 carbon atoms, phenyl, or phenyl substituted with lower alkyl or lower alkoxy, and wherein each n is independently 1 or 2;

and further wherein the polyvalent linking moiety is either comprised of at least 2 linker functional groups capable of covalently bonding to specific binding

peptides or technetium-99m binding moieties, wherein at least 2 of the linker functional groups are identical, and wherein a multiplicity of polyvalent linking moieties are covalently linked to form a branched polyvalent linking moiety; or
is selected from *bis*-succinimidylmethylether, 4-(2,2-dimethylacetyl)benzoic acid, N-[2-(N',N'bis(2-succinimidoethyl)aminoethyl)]-N^6,N^9-bis(2-methyl-2-mercaptopro-pyl)-6,9-diazanonanamide, *tris*(succinimidylethyl)amine, *bis*-succinimido-hexane, 4-(O-CH_2CO-Gly-Gly-Cys.amide)acetophenone or a derivative thereof;

with the proviso that the reagent is neither of the following structures:
$[Pic.SC_{Acm}SYNRGDSTC.amide]_3$-TSEA;
$(GPRPC_{Acm}GC_{Acm}C.amide)_3$-TSEA
$[(GPRP)_2K]_2KC_{Acm}GC_{Acm}$amide;

6. A complex formed by reacting a reagent of any one of the claims 1 to 5 with technetium-99m in the presence of a reducing agent, optionally dithionite ion, stannous ion or ferrous ion, or by labeling said reagent with technetium-99m by ligand exchange of a prereduced technetium-99m complex.

7. A kit for preparing a radiopharmaceutical preparation containing a predetermined quantity of a reagent of any one of claims 1 to 5 and a sufficient amount of a reducing agent to label the reagent with technetium-99m.

8. A method for labeling a reagent according to any one of claims 1 to 5 comprising reacting the reagent with

technetium-99m in the presence of a reducing agent, optionally dithionite ion, stannous ion or ferrous ion.

9. The use of a reagent of any one of claims 1 to 5 for the manufacture of a medicament for imaging a site within a mammalian body.

10. A reagent having a formula selected from the following, and optionally radiolabeled with technetium-99m:

(*acetyl*.F_DPRPG)$_2$KGGGCamide

(GPRVVERHQSA)$_2$KC_{Acm}GC_{Acm}amide

(CH_2CO.Y_D.Apc.GDCGGC$_{Acm}$GC$_{Acm}$GGCamide)$_2$-BSME

S

(*acetyl*.CC_{Acm}GC_{Acm}GGPLYKKIIKKLLES)$_2$-BSME

(CC_{Acm}GC_{Acm}GGRGDS)$_3$-TSEA

(RALVDTLKGGC$_{Acm}$GC$_{Acm}$Camide)$_3$-TSEA

(ma.GGGRALVDTLKFVTQAEGAKamide)$_2$-[BAT-BS]

(GRGDFC$_{Acm}$GC$_{Acm}$Camide)$_3$-TSEA

(Pic.GC$_{Acm}$RALVDTLKFVTQAEGAKCamide)$_3$-TSEA

(*acetyl*.SYNRGDTC$_{Acm}$GC$_{Acm}$Camide)$_2$-DMAB

11. An article comprising a sealed vial containing a predetermined quantity of a reagent of claim 10 and a sufficient amount of reducing agent to label the composition with technetium-99m.

12. A pharmaceutical composition suitable for injection comprising a diagnostically effective amount of a reagent as defined in any one of claims 1 to 5 and a pharmaceutically acceptable carrier."

(i) auxiliary request 7:

" 1. A reagent for preparing a scintigraphic imaging agent for imaging sites within a mammalian body comprising a multiplicity of specific-binding peptide moieties, each specific-binding peptide having an amino acid sequence of 3 to 100 amino acids, covalently linked to a polyvalent linking moiety, and a technetium-99m binding moiety covalently linked to a plurality of the specific-binding peptides, the polyvalent linker moiety, or both, said reagent optionally being radiolabeled with technetium-99m, wherein the reagent is selected from the group consisting of :

(*acetyl*.F_DPRPG)$_2$KGGGCamide

(GPRVVERHQSA)$_2$K$C_{Acm}GC_{Acm}$amide

(CH_2CO.Y_D.Apc.GDC$GGC_{Acm}GC_{Acm}$GGCamide)$_2$-BSME

(*acetyl*.$CC_{Acm}GC_{Acm}$GGPLYKKIIKKLLES)$_2$-BSME

($CC_{Acm}GC_{Acm}$GGRGDS)$_3$-TSEA

(RALVDTLKG$GC_{Acm}GC_{Acm}$Camide)$_3$-TSEA

(ma.GGGRALVDTLKFVTQAEGAKamide)$_2$-[BAT-BS]

(GRGDF$C_{Acm}GC_{Acm}$Camide)$_3$-TSEA

(Pic.GC_{Acm}RALVDTLKFVTQAEGAKCamide)$_3$-TSEA

(*acetyl*.SYNRGDT$C_{Acm}GC_{Acm}$Camide)$_2$-DMAB

".

VIII. The appellant-opponent's arguments, presented in writing, can be summarised as follows:

The subject-matter of the claims did not meet the requirements of Article 84 EPC, as terms like "TSEA", "Acm", "BSME", "BAT-BS" and "DMAB" were not clear. Moreover, the definition of structure II was not clear either. As for novelty, it was held that documents (9), in so far as its priority was valid, (1) and (6) were pertinent for novelty. In connection with document (1),

it was held that DTPA was suitable for binding ^{99m}Tc. In addition, the subject-matter of the claims lacked an inventive step over document (1) or (2) in combination with document (4), or, alternatively, over document (5).

IX. The appellant-patentee's arguments can be summarised as follows:

With regard to the clarity objections, it was held that the terms used in the claims, e.g. TSEA were clear for the skilled person. As for the objections raised in connection with formula II, it was emphasised that the alleged unclarity had not been caused by amendments made in the course of the opposition or appeal proceedings; as a consequence, the board was not entitled to address them. Regarding novelty in connection with document (1) and (2), respectively, it was held that DTPA was not suitable for binding ^{99m}Tc. Neither document (6) nor document (9), in so far as the priority was valid, disclosed reagents comprising a multiplicity of specific binding peptides. Document (9) contained some specific reagents comprising a multiplicity of specific binding peptides, which, however, had all been disclaimed. In connection with inventive step, the appellant-patentee emphasised that the central teaching of the patent in suit consisted in the provision of reagents for scintigraphic imaging, where the ^{99m}Tc-binding moiety, the polyvalent linking moiety and the specific binding peptide moiety were arranged as separate units, which allowed high flexibility without influencing the complexing efficacy. None of the documents on file, either alone or in combination rendered this concept obvious. Moreover, the skilled person would not combine the teaching of document (2) with that of document (3)

or (4) in view of the considerable structural differences between peptides and proteins. In connection with auxiliary request 6a, the appellant-patentee additionally emphasised that the polyvalent linking moieties were arranged as to create branching, which was not disclosed in any of the available prior art documents.

X. The appellant-patentee requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main request filed with letter of 19 April 2007; or on the basis of one of auxiliary requests 1 to 3 filed with letter of 5 November 2007; or on the basis of one of new auxiliary requests 4 to 6 filed during the oral proceedings; or on the basis of auxiliary request 6a filed during as auxiliary request 5 with letter of 5 November 2007: or on the basis of auxiliary request 7 filed during the oral proceedings.

The appellant-opponent had requested in writing that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

1. The appeal is admissible.

2. Main request:

2.1 Article 84:

When amendments are made to a patent during an opposition, Article 102(3) EPC requires consideration as to whether the amendments introduce any contravention of any requirement of the Convention, including Article 84 EPC; Article 102(3) EPC does, however, not allow objections to be based upon Article 84 EPC, if such objections do not arise out of the amendments made.

As for formula II, the board notes that it is present in claim 2 as granted. The same applies to the terms "TSEA", "Acm", "BSME", "BAT-BS" and "DMAB", which can be found in claim 14 as granted. As a consequence, the board is not competent to deal with these clarity objections.

2.2 Novelty of claim 1:

Document (9) was filed on 21 May 1993 and published on 25 November 1993. Its priority date is 21 May 1992. It therefore forms state of the art according to Article 54(3) and (4) EPC to the extent that its priority is valid. Claim 1 of document (9) relates to a reagent for preparing a scintigraphic imaging agent for imaging a thrombus within a mammalian body comprising a specific binding compound capable of binding to at least one component of a thrombus, covalently linked to a technetium-99m binding moiety, wherein the technetium-99m binding moiety has the formula: $C(pgp)^s$-(aa)-$C(pgp)^s$ wherein $C(pgp)^s$ is a cysteine having a protected thiol group and (aa) is an amino acid. This formula corresponds to formula I of the present main request. Claim 6 of document (9) defines the specific binding compound as a peptide comprising 4 to 100 amino acids.

Moreover, a polyvalent linking moiety is also disclosed in document (9), as the technetium-99m binding moiety and the specific binding compound are linked via an amino acid (claim 3). The subject-matter as defined above enjoys the priority of 21 May 1992 (see document (16): claims 1 to 3).

It therefore has to be evaluated whether document (9) specifically relates to a multiplicity of specific binding compounds, which is the only potentially distinguishing feature of present claim 1. As was shown above, claim 1 of document (9) defines a "reagent… comprising **a** specific binding compound…" [emphasis by the board]. In order to determine whether this definition limits the specific disclosure of document (9) to reagents comprising only a single specific binding compound, as was alleged by the appellant-patentee, or whether the specific disclosure of document (9) includes reagents comprising more than one specific binding compounds, it is necessary to look at the list of individual compounds. Table I of document (9) contains a number of specific reagents including several compounds comprising more than one specific binding peptide moieties (see e.g. $C_{Acm}GC_{Acm}$GGRGDGGRGDS, $C_{Acm}GC_{Acm}$GGRGDGGRGDGGRGDS, GRGDVRGDFK$C_{Acm}GC_{Acm}$.amide and GRGDVRGDF$C_{Acm}GC_{Acm}$.amide, which can also be found in Table I of document (16)). In view of the presence of numerous preferred embodiments with more than one specific binding moiety in documents (9) and (16), the board came to the conclusion that the person skilled in the art would understand the passage "reagent… comprising **a** specific binding compound…" as meaning "reagent… comprising **one or more** specific binding compound(s)…", which includes a multiplicity of specific binding

moieties. Therefore, in order to establish novelty over document (9), it is not sufficient to specifically disclaim the individual compounds with more than one specific bonding moieties as was done in claim 1 of the present main request. As a consequence, the subject-matter of claim 1 does not meet the requirements of Article 54 EPC.

2.3 As regards inventive step, see point 9.4.3 below (paragraph 2).

3. Auxiliary request 1:

As compared to claim 1 of the main request, claim 1 of auxiliary request 1 contains the additional feature that said specific binding peptide accumulates at an organ, a tumor, a thrombus site or a site of infection. As the reagents of document (9) and the corresponding priority document (16) are used for the scintigraphic imaging of thrombi (see page 1, first paragraph of documents (9) and (16)), their specific binding peptides necessarily accumulate at the thrombus site. As a consequence, the subject-matter of claim 1 of auxiliary request 1 also lacks novelty (Article 54 EPC). Reference is made to paragraphs 2.2 and 2.3 above, which apply *mutatis mutandis* to auxiliary request 1.

4. Auxiliary request 2:

As compared to claim 1 of the main request, claim 1 of auxiliary request 2 is now reformulated as a "Swiss-type" claim. In view of the fact that the reagents of document (9) and the corresponding priority document (16) are used for the scintigraphic imaging of thrombi (see

page 1, first paragraph of documents (9) and (16)), the subject-matter of claim 1 of auxiliary request 2 also lacks novelty (Article 54 EPC). Reference is made to paragraphs 2.2 and 2.3 above, which apply *mutatis mutandis* to auxiliary request 2.

5. Auxiliary request 3:

As compared to claim 1 of the main request, claim 1 of auxiliary request 3 is now directed to kits additionally comprising a sufficient amount of a reducing agent to label the reagent with technetium-99m. As document (9) and the corresponding priority document (16) also disclose kits comprising a sufficient amount of a reducing agent to label the reagent with technetium-99m (see document (9), page 18, lines 25-28 and document (16), page 10, lines 5-9), the subject-matter of claim 1 of auxiliary request 3 is not novel either (Article 54 EPC). Reference is made to paragraphs 2.2 and 2.3 above, which apply *mutatis mutandis* to auxiliary request 3.

6. Auxiliary request 4:

6.1 Admissibility:

Auxiliary request 4 was filed at a late stage of the second oral proceedings of 1 October 2008. As compared to the previous auxiliary request 4, which had been filed with letter of 5 November 2007, claim 1 was further amended by additionally deleting formulae IV and V. This deletion was a direct reaction to inventive step objections based on a combination of document (2) with documents (3) or (4), which had been raised by the board at the oral proceedings. Therefore, and in view of the

fact that the simple deletion of some of the formulae of claim 1 could not take the appellant-opponent by surprise, the board decided to admit auxiliary request 4 to the proceedings.

6.2 Novelty of claim 1:

In view of the fact that the disclosure of document (9) as described in paragraph 2.2 above is detrimental to the novelty of reagents corresponding to formula I ($C(pgp)^s$-(aa)-$C(pgp)^s$), the deletion of other formulae of claim 1 cannot establish novelty. As a consequence, the subject-matter of claim 1 of auxiliary request 4 is not novel either (Article 54 EPC). Reference is made to paragraph 2.3 above, which applies *mutatis mutandis* to auxiliary request 4.

7. Admissibility of auxiliary request 5:

Auxiliary request 5 was filed at a late stage of the second oral proceedings of 1 October 2008. In claim 1, a disclaimer was introduced in order to establish novelty over document (9), which means that this new request was a reaction to objections already raised by the appellant-opponent in his notice of appeal (see point III of the notice of appeal). As this request could have been filed much earlier and as the board had *prima facie* objections in connection with the requirements of Article 84 EPC in view of the fact that the patent in suit does not appear to contain any information about how the specific binding peptide moiety must be structured in order to specifically bind or not to bind to a thrombus in vivo, the board did not admit auxiliary request 5 into the proceedings.

8. Admissibility of auxiliary request 6:

Auxiliary request 6 was also filed at a late stage of the second oral proceedings of 1 October 2008. This request is identical with auxiliary request 5 filed with letter of 5 November 2007, except that the feature "…comprised of at least 2 linker functional groups capable of covalently bonding to specific binding peptides or technetium-99m binding moieties, wherein at least 2 of the linker functional groups are identical" was deleted from claim 1. This deletion was not caused by any new facts or arguments. Moreover, the board sees *prima facie* problems with Article 123(2) EPC, as the feature "… wherein a multiplicity of polyvalent linking moieties are covalently linked to form a branched polyvalent linking moiety" appears to be disclosed only in combination with the deleted feature cited above (see claim 9 of the application as filed, which refers to claim 6 which in its turn refers to claim 1). As a consequence, auxiliary request 6 is not admitted.

9. Auxiliary request 6a:

9.1 Admissibility:

Auxiliary request 6a is identical with auxiliary request 5 filed with letter of 5 November 2007. It is therefore admissible.

9.2 Formal requirements:

Amended claim 1 is based on claims 1-3, 6, 9 and 28 as originally filed. The compounds disclaimed correspond to

reagents disclosed in post-published document (9). As a consequence, the requirements of Article 123(2) EPC are met. Moreover, the amendments made constitute a restriction as compared to the claims as granted, so that the requirements of Article 123(3) EPC are also met. Finally, the amendments introduced into claim 1 did not give rise to any unclarities so that no objections are raised under Artice 84 EPC either.

9.3 Novelty:

9.3.1 Novelty over document (9):

Apart from the three specific compounds which are disclaimed, document (9), to the extent that its priority is valid, does not specifically disclose a branched polyvalent linking moiety as defined in present claim 1 or one of the specific polyvalent linking moieties claimed therein. The subject-matter of claim 1 and dependent claims 2-5 is therefore novel over the disclosure of document (9). The same applies *mutatis mutandis* to independent claims 6-9 and 12.

Neither does document (9) to the extent that its priority is valid, disclose a reagent as claimed in independent claim 10, so that the subject-matter of claim 10, and as a consequence that of dependent claim 11 is also novel.

9.3.2 Novelty over document (1):

Document (1) does neither disclose any of technetium-99m binding moieties as defined in formulae I-V nor the polyvalent linking moieties of claim 1 nor does it

disclose a specific compound as defined in claim 10. The subject-matter as claimed in auxiliary request 6a is therefore novel over document (1).

9.3.3 Novelty over document (6):

In the statement of the grounds of appeal, the appellant-opponent also cited document (6) in connection with novelty. Document (6) was filed on 31 December 1992 and published on 8 July 1993. Its eldest priority date is 3 January 1992. It therefore forms state of the art according to Article 54(3) and (4) EPC to the extent that its priority is valid.

The appellant-opponent held that the peptides of document (6) comprising the structure R_1-[Cys-(R_2)-Cys]-R_3, wherein R_2 is an amino acid sequence containing from 1 to 20 amino acid residues, and wherein R_1 and R_2 represent a biological function domain including IKVAV or YIGSR anticipate the subject-matter as claimed (see claims 4 and 6 of document (6)). Although the sequence R_1-[Cys-(R_2)-Cys]-R_3 includes technetium-99m binding moieties as defined in claim 1 of auxiliary request 6a, document (6) does not appear to disclose peptides comprising this structure in combination with a the polyvalent linking moieties as now claimed. Nor does document(6) disclose a reagent as claimed in claim 10. Therefore the subject-matter of auxiliary request 6a is novel over document (6), irrespective of the question whether or not the priority of document (6) is valid.

9.3.4 It follows from this that the subject-matter of auxiliary request 6a meets the requirements of Article 54 EPC.

9.4 Inventive step:

9.4.1 The present invention concerns reagents for scintigraphic imaging, which specifically bind to targets *in vivo* and which efficiently bind the element ^{99m}Tc. The reagents are characterised by specific technetium-99m binding peptides and by a multiplicity of peptides comprising from 3 to 100 amino acids, which specifically bind to defined parts of the body and which are linked to the specific technetium-99m binding peptide by a specific linker agent or by a multiplicity of polyvalent linking moieties, which are arranged such that branching occurs (see page 1, lines 21-28 and paragraph bridging pages 10 and 11 of the application as filed).

9.4.2 Document (2) also discloses reagents for scintigraphic imaging in the form of *bis*MSH-DTPA comprising two tridecapeptides (MSH), which selectively bind to murine melanotic melanoma, and diethylenetriamine pentaacetic acid (DTPA), which can stably bind ^{111}In but is not very efficient in binding ^{99m}Tc (see pages 112 and the paragraph bridging pages 116 and 117. Document (2) constitutes the closest prior art. With regard to this prior art, the problem to be solved can be seen in providing a reagent for scintigraphic imaging which binds ^{99m}Tc more effectively and which provides more structural flexibility without impeding the binding efficiency of the technetium-99m binding moiety. This problem was solved by replacing DTPA by a compound as

defined by formulae I - VI and by adding a polyvalent linking moiety of present claim 1 or by selecting a reagent as defined in present claim 10.

In the light of the examples and in particular of example 5, the board is satisfied that the above problem was indeed solved.

9.4.3 Inventive step of claim 1:

As can be seen from the paragraph above, the solution of the problem comprises two aspects: firstly, the replacement of DTPA by a compound according to formulae I - VI, and secondly, the introduction of a polyvalent linking moiety.

Regarding the first aspect, the board came to the conclusion that the replacement of DTPA by a compound according to formula I or II is obvious, as the technetium-99m binding capacity of such compounds is known from documents (3) and (4). This was extensively discussed at the second oral proceedings in connection with the main request and auxiliary requests 1-3, which, apart from lacking novelty over the interfering document (9) were also found to lack an inventive step over the combination of document (2) with document (3) and (4), respectively.

As far as the second aspect is concerned, the person skilled in the art, starting from document (2) and trying to find a more efficient ^{99m}Tc binding moiety, gets the information to replace DTPA by a diaminedithiol as disclosed in document (3) (see document (2), paragraph bridging pages 116 and 117) but gets no

guidance at all as to the arrangement of the various moieties within the molecule. Starting from *bis*MSH-DTPA, he would therefore simply replace DPTA and thus arrive at an unbranched structure, where the two MSH chains are directly linked by the ^{99m}Tc binding moiety. The concept of adding polyvalent linking moieties which are arranged such that branching occurs is not rendered obvious by document (2), either alone or in combination with documents (3) or (4). Said branching allows enhanced flexibility in that the ratio of ^{99m}Tc binding moieties to specific binding peptide moieties within the molecule can be easily varied without impeding the binding capacity of the ^{99m}Tc binding moiety. It is additionally noted that the concept of branching is also materialised by the specific polyvalent linking moieties listed at the end of claim 1. As a consequence, the subject-matter of claim 1 and of dependent claims 2-5 involves an inventive step.

9.4.4 The reasoning of paragraph 9.4.3 above applies *mutatis mutandis* to independent claims 6-9 and 12, which therefore also meet the requirements of Article 56 EPC.

9.4.5 Inventive step of claims 10-11:

As each of the specific reagents of claim10 is branched, the reasoning of paragraph 9.4.3 above applies *mutatis mutandis* to independent claim 10 and, as a consequence, also to dependent claim 11.

9.5 The ground of opposition raised under Article 100(a) EPC in combination with Article 52(4) EPC was not maintained in the appeal procedure. The board, however, is satisfied that the subject-matter as claimed in

auxiliary request 6a meets the requirements of Article 52(4) EPC.

10. In view of the amendments made, the board finds it appropriate, in accordance with Article 111(1) EPC, to remit the case to the first instance for adaptation of the description.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent in amended form on the basis of auxiliary request 6a filed as auxiliary request 5 with letter of 5 November 2007 and a description to be adapted accordingly.

The Registrar: The Chairman:

N. Maslin J. Riolo