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Datasheet for the decision of 30 September 2008

Case Number: T 1220/07 - 3.3.02

Application Number: 93901469.2

Publication Number: 0614379

IPC: A61K 51/08

Language of the proceedings: EN

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

Patentee:
CIS bio international

Opponent:
BRACCO IMAGING S.p.A.

Headword:
Technetium labelled peptide/CIS BIO

Relevant legal provisions:
-

Relevant legal provisions (EPC 1973):
EPC Art. 100(c)

Keyword:
"Amendments - added subject-matter (yes); added feature not clearly and unambiguously disclosed"

Decisions cited:
G 0001/93

Catchword:
-

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Case Number: T 1220/07 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 30 September 2008

Appellant: (Patent Proprietor)	CIS bio international RN 306 Saclay B.P. 32 F-91192 Gif sur Yvette Cedex (FR)
Representative:	Dörries, Hans Ulrich df-mp Fünf Höfe Theatinerstrasse 16 D-80333 München (DE)
Respondent: (Opponent)	BRACCO IMAGING S.p.A. Via Egidio Folli, 50 I-20134 Milano (IT)
Representative:	Sheard, Andrew Gregory Patent Attorney P.O. Box 521 Berkhamsted Herts. HP4 1YP (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 27 April 2007 revoking European patent No. 0614379 pursuant to Article 102(1) EPC 1973.**

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
J. Van Moer

Summary of Facts and Submissions

I. European patent No. 614 379, based on international patent application PCT/US92/10716 and filed at the EPO as WO 93/10747, was granted with ten claims.

Independent claims 1 and 9 of this patent read as follows:

"1. A method for preparing a scintigraphic imaging agent comprising the step of reacting technetium-99m and a reducing agent with a peptide for imaging targeting sites within a mammalian body, said peptide having between 4 and 100 amino acids and being covalently linked to a technetium-99m complexing group comprising a thiol moiety being in the reduced form and having the structure:

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

wherein

A is H, HOOC, H_2NOC, (peptide)-NHOC, (peptide)-OOC or R^4;
B is H, SH, $-NHR^3$, $-N(R^3)$-(peptide), or R^4;
X is H, SH, $-NHR^3$, $-N(R^3)$-(peptide), or R^4;
Z is H or R^4;
R^1, R^2, R^3, and R^4 are independently H or lower straight or branched chain or cyclic alkyl;
n is 0, 1 or 2;
and
where B is $-NHR^3$ or $-N(R^3)$-(peptide), X is SH, and n is 1 or 2;
where X is $-NHR^3$ or $-N(R^3)$-(peptide), B is SH, and n is 1 or 2;

where B is H or R^4, A is HOOC, H_2NOC, (peptide)-NHOC or (peptide)-OOC, X is SH, and n is 0 or 1;
where A is H or R^4, then where B is SH, X is $-NHR^3$ or $-N(R^3)$-(peptide)
and
where X is SH, B is $-NHR^3$ or $-N(R^3)$-(peptide);
where X is H or R^4, A is HOOC, H_2NOC, (peptide)-NHOC or (peptide)-OOC and B is SH;
where Z is methyl, X is methyl, A is HOOC, H_2NOC, (peptide)-NHOC or (peptide)-OOC, B is SH and n is 0;

wherein the technetium-99m complexing group contains a single thiol.

9. A scintigraphic imaging agent comprising a peptide for imaging targeting sites within a mammalian body, said peptide having between 4 and 100 amino acids and being covalently linked to a technetium-99m complexing group comprising a thiol moiety having the structure:

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

wherein

[same variations as in claim 1]

wherein the technetium-99m complexing group contains a single thiol and is labeled with technetium-99m;

with the proviso that when the technetium-99m complexing group is cysteine or a cysteine linked to a peptide, then
a) the peptide if having between 4 and 50 amino acids does not contain the amino acid sequence LDV, or

b) the peptide if having between 4 and 100 amino acids does not contain the amino acid sequence EPPT."

II. Opposition was filed against the granted patent *inter alia* under Article 100(c) EPC 1973.

The following document was cited *inter alia* during the proceedings before the opposition division and the board of appeal:

(9) declaration of Ms Linder of 26 February 2007, attached to the letter of the opponent dated 27 February 2007 during the opposition proceedings

III. By its decision, posted on 27 April 2007, the opposition division revoked the patent under Article 102(1) EPC 1973.

The opposition division held that neither the set of claims of the main request, which consisted of the claims as granted, nor the set of claims of auxiliary requests 1 to 3 met the requirements of Articles 100(c) and 123(2) EPC 1973 respectively.

It noted that the condition that "the technetium-99m complexing group" contained a single thiol was added matter with respect to the application as filed, since originally only the "thiol moiety" covering up to two of four complexing groups for technetium-99m was defined and not the whole complexing group.

In detail, the arguments were:

"2.3 In order to determine whether or not an amendment offends against Art. 123(2) EPC it has to be examined whether technical information has been introduced which a skilled person would not have objectively and unambiguously derived from the application as filed.

2.4 In this respect, claim 1 as originally filed relates to a peptide having between 4 and 100 amino acids and being covalently linked to a technetium-99m complexing group comprising a thiol moiety having the structure as given by the general formula of said claim [being the same as in claim 9 as granted; addition by the board].

For a complex, at least two additional amino acids are required to provide the appropriate coordination chemistry to form a stable complex with technetium. Technetium needs four coordinating atoms of which only two are defined in the thiol moiety represented by the general formula of claim 1, namely X and B.

According to claim 1 as filed, B and/or X may represent thiol. Thus there is a clear disclosure that the thiol moiety may contain a single thiol group, but it is also clear that the thiol moiety represents only a part of the complexing group and does not constitute the complexing group itself.

2.5 Original claim 1 defines with detail the structural requirements of the thiol moiety without specifying the structural requirements of the elements of the Tc-99m complexing group other than the thiol moiety. Claim 1

as originally filed allows thus any residue (including a thiol one) as the remaining part of the Tc-99m complexing group.

2.6 The description of the original application does not contain any indications on the nature of the residues/aminoacids providing the remaining complexing groups. There is no clear and unambiguous disclosure in the description that the entire complexing group contains only a single thiol group, in other words that those remaining elements can be any other possible functional group except a thiol group. In this respect, it is pointed out that the application as filed related also to reagents where the complexing group contains a thiol moiety with more than one thiol group within said thiol moiety.

2.7 Consequently, the Opposition Division is of the opinion that the meaning "single thiol complexing group" is disclosed in the original application only as part of the structure of the seven individual compounds of Table I and original claim 17.

Thus, it has to be established whether or not those particular individual compounds form the proper basis for generalising the concept of single thiol complexing group to any peptide covered by claim 1.

2.8 Although examples do form part of the "content of the application as filed" and therefore need to be considered when deciding the question what information is clearly and unambiguously derivable from that content, in contrast to a generically defined group or class of chemical compounds, in which the meaning of

the substituents is variable, an individual chemical entity only discloses its structural elements in their specific combination, to the exclusion of any such variability.

2.9 In the present case, the seven particular individual compounds comprise in their structure a specific "single thiol" complexing group, exclusively linked to a particular targeting peptide. However, the complexing group is not explicitly identified as such in any of the exemplified peptides. Moreover, the application as filed neither draw attention to the fact that the exemplified complexing groups contain a single thiol. The application as filed also contains no indication as to which elements of the exemplified peptides may be varied and which must be retained unchanged.

Thus the skilled person would not have recognised without any doubt from the original disclosure that peptides with a complexing group as presently claimed were foreseen as a possible fall back position.

Accordingly, in the Opposition Division's view, the skilled person derives from the structure of those seven particular individual peptides nothing more than the bare disclosure of the structural elements in their particular combination, namely a specific complexing group to be linked to a particular targeting peptide.

Therefore, the original disclosure of those seven individual peptides cannot support the more generalised limitation indicated in claims 1, 7 and 9 [as granted; addition by the board] for the complexing group.

2.10 In view of the forgoing, it is the Opposition Division's opinion that the present feature "the technetium-99m complexing group contains a single thiol" is not disclosed in the originally filed application document and constitutes added subject-matter contrary to Article 123(2) EPC."

IV. The patentee (hereafter appellant) lodged an appeal against said decision and filed grounds of appeal together with the request to maintain the patent as granted.

V. On 30 September 2008, oral proceedings took place before the board.

VI. During these oral proceedings the appellant sought to file an auxiliary request.

It argued that it was admissible, though late-filed, because it was restricted to the examples and to the subject-matter of claim 17 as originally filed; therefore the condition that "the technetium-99m complexing group contains a single thiol", which was the point of the discussion in the proceedings as held so far, had been removed. Consequently the set of claims of the auxiliary request was clearly allowable.

VII. With respect to the allowability of the main request, the appellant mainly argued that the conclusions of the opposition division were not correct, since the questioned provision was to be derived clearly and unambiguously from the application as originally filed.

For the skilled person it was clear that absolutely all information on thiol groups as part of the complexing group, consisting of four complexing ligands, was contained in the definition of the thiol moiety, and the restriction to one of them together with the restriction to one thiol group within that thiol moiety was clearly disclosed.

Corresponding to that, but also from the teaching as originally filed, it was clear that the complexing ligands not defined by the provisions disclosed with respect to the thiol moiety had to be provided for by the N-atoms of the skeleton of peptides being present. The skilled person would not have contemplated any complexing thiol group outside of the thiol moiety because such complexing thiol groups would normally build technetium-99m complexes which are less stable than those including N-atoms from the peptide backbone.

To find examples of technetium-99m complexing groups containing thiol groups outside the thiol moiety as defined in the application as filed, special selections always were necessary.

Additionally, all examples were in conformity with the condition of a technetium-99m complexing group containing a single thiol.

In writing, the appellant had submitted that the disputed condition that the "technetium-99m complexing group contains a single thiol" found support in the original claims as remaining a generic group of compounds differing from the original group only by its smaller size, that this condition was a limiting

feature in line with G 1/93 (OJ EPO 1994, 541) and that it was acceptable as an admissible generalisation from the examples.

VIII. The respondent's arguments may be summarised as follows:

The auxiliary request as introduced by the appellant was not admissible because it raised problems with respect to Articles 84 and 100(c) EPC 1973 at first glance. For instance, there was a difference between claim 17 as originally filed, which was a product claim, and new claim 1, which referred to a method of preparation, but comprising the same substance as was referred to in original claim 17.

In the respondent's view, the opposition division was right in its decision with respect to the patent as granted, because the application as originally filed provided for no information on complexing ligands complementing the one or two ligands provided for by the thiol moiety to arrive at the compulsory four ligand surroundings of technetium-99m. On the other hand, the subject-matter of the patent as granted was restricted to one single thiol group in the whole complexing group of technetium-99m, which meant, as added information, that three of the four complexing ligands had to be free of sulphur.

IX. The auxiliary request which the appellant sought to introduce during the oral proceedings was not admitted into the proceedings.

X. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained

as granted or, in the alternative, on the basis of the auxiliary request submitted during the oral proceedings. He further requested remittal to the first instance for further prosecution.

The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. The set of claims which the appellant sought to introduce during the oral proceedings as an auxiliary request was late-filed.

It did not provide an answer to newly-raised arguments and could have been submitted at any time during the procedure before the opposition division and before the board.

Additionally, it was not prima facie allowable because of various problems with regard to clarity and original disclosure, and the claims were amended in a way that required a highly complex further assessment.

Therefore, the board exercised its discretion and did not admit the request into the proceedings.

3. With respect to the main request, the board sees no reason to differ from the arguments and conclusion of the opposition division (see point III of this decision).

The condition "wherein the technetium-99m complexing group contains a single thiol" cannot be derived **clearly and unambiguously** from the application as filed and extends the content of the application. Claim 9 of the set of claims of the main request (claims as granted) does not fulfil the requirements of Article 100(c) EPC 1973.

4. In the circumstances of the case, the arguments of the appellant cannot succeed:

4.1 It was of the opinion that after having - in concordance with Article 123(2) EPC 1973 - restricted the presence of "a thiol moiety" to the presence of "one single thiol moiety" and the number of thiol groups in this thiol moiety to one, it was perfectly clear that the complexing ligands other than the thiol group from the thiol moiety had to be provided for by the N-atoms of the skeleton of some peptide being present.

The appellant further stated during the oral proceedings that, in case the substituents in the general formula of claim 9 as granted contained no peptide, and the only peptide being present was one containing four amino acids as defined by the wording "comprising a peptide for imaging targeting sites within a mammalian body, said peptide having between 4 and 100 amino acids and being covalently linked to a technetium-99m complexing group ...", the consequence simply was that two of the four amino acids were involved in the complexing group and only two amino acids were left outside the complexing group to fulfil

the task of binding the technetium-99m labeled unit to the targeting site (for instance an organ in the mammalian body).

But this statement during the oral proceedings is in contrast to the claims and the description of the granted patent and to the application as originally filed. There, the appellant explicitly ruled out that the "peptide having between 4 and 100 amino acids" could be part of the complexing group, since the said peptide has to be covalently **linked to** the complexing group. In this way it is indicated by the relevant claims and description that the "peptide having between 4 and 100 amino acids" had to be present in addition to the complexing group and not as part of it (see for instance page 5, lines 25 to 28 of the application as filed and page 3, line 58 to page 4, line 2 of the patent specification).

With this situation, it is clear for the board that at least two of the ligands in fact were free to any reasonable choice of the skilled person in the sense of the opposition division's decision and that the "single thiol" teaching that the appellant suggested with respect to the four ligands of the technetium-99m complexing group could not be drawn from the application as filed. Thus the opposition division's decision so far is approved by the board.

4.2 Even the appellant's submission that the effort and the precision, the appellant had lent to the definition of the thiol moiety clarified that he had not wanted to let other thiol groups be present in a totally undefined manner within the technetium-99m complexing

group, does not lead to the clear and unambiguous teaching that this must be true. It is only a question of probability or maybe plausibility that the teaching could be meant in that way, but not a sound and safe basis for a conclusion to be drawn with respect to fulfilling the provisions of Article 100(c) EPC 1973 or not.

4.3 The same holds for the appellant's submission that peptides containing more than one thiol group in the complexing group within the meaning of claim 1 as originally filed always needed particular steps of selection to be found even in contradiction to the way in which the most stable ones would be defined. The most stable arrangement of the four ligands in the technetium-99m complexing group namely was with all the ligands constituting an atom within five-membered rings, while thiol-containing arrangements outside the thiol moiety normally contained the thiol group in six-membered rings (for illustration see declaration (9), pages 1 and 2).

This argumentation, however, only means that such peptides containing technetium-99m complexing groups that contain thiol groups in addition to the thiol moiety **are members of the pool** defined by claim 1 as originally filed and that they are at most slightly different to others and not as perfect as the best ones of the pool. But it is no argument that their non-existence with respect to the teaching of this claim is clearly and unambiguously **disclosed as a preferred subject-matter** to allow for the teaching of the "technetium-99m complexing group containing a single thiol".

4.4 The appellant's argument that during the proceedings only a generic group had been reduced to one of a smaller size cannot hold either.

The board notes that with respect to the definition of the complexing atoms constituting the technetium-99m complexing group in addition to the thiol moiety, there was no generic information in the application as filed that contained a group of defined substituents to make a choice within. Such a group could have been reduced in size. In the case in suit, however, instead of this generic information there was no information on the possible complexing atoms at all in the application as filed. This "missing information" in claim 9 of the patent as granted had been changed to the positive information that the complexing atoms constituting the technetium-99m complexing might be anything plausible, but no other thiol group than the first and single one contributed by the thiol moiety.

4.5 In the board's ruling, the provision that the "technetium-99m complexing group contains a single thiol" can also not be found to be a limiting feature in line with decision G 1/93, OJ EPO 1994, 541.

In contrast to the submission of the appellant, for instance in part II of the headnote of the above decision of the Enlarged Board of Appeal, there is the clear provision that this feature only "**without providing a technical contribution** to the subject-matter of the claimed invention, merely limits the protection conferred by the patent as granted by excluding protection for part of the subject-matter of

the claimed invention as covered by the application as filed" in order "not to be considered as subject-matter which extends beyond the content of the application as filed within the meaning of Article 123(2) EPC".
But an atom being part of a complexing group or not is technical information and so this condition of decision G 1/93 does not apply in the current case.

4.6 *Generalisation from the examples*

In addition to the arguments of the opposition division it is pointed out in this context that generalisation from examples is possible if the characteristics in question clearly refer to the more general context, meaning in the case in suit the embodiments of claim 9 as granted. Such information is missing in the application as filed with respect to the "technetium-99m complexing group containing a single thiol".

5. Since from the argumentation and conclusion of this decision independent claim 9 as granted, being subject-matter of the main request, does not meet the requirements of Article 100(c) EPC 1973, there is no need to consider the other claims of the main request, which is the only request admitted to the proceedings for decision by the board.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald