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**Datasheet for the decision
of 1 October 2015**

Case Number: T 0788/14 - 3.3.04

Application Number: 01974480.4

Publication Number: 1324771

IPC: A61K39/395, C07K19/00

Language of the proceedings: EN

Title of invention:

Therapeutic and tolerance inducing antibodies

Patent Proprietor:

Isis Innovation Limited

Opponent:

Mintz Levin Cohn Ferris Glovsky and Popeo
Intellectual Property LLP

Headword:

Tolerogenic therapeutic antibody/ISIS

Relevant legal provisions:

EPC Art. 100 (c)

Keyword:

Main request - subject-matter extends beyond the content of
the application as filed (no)

Remittal to the department of first instance - (yes)

Decisions cited:

Catchword:



Beschwerdekammern
Boards of Appeal
Chambres de recours

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Case Number: T 0788/14 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 1 October 2015

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 7 February 2014
revoking European patent No. 1324771 pursuant to
Article 101(2) and 101(3) (b) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: R. Morawetz
 M. Blasi

Summary of Facts and Submissions

- I. The appeal by the proprietor (hereinafter "appellant") lies against the decision of the opposition division revoking European patent No. 1 324 771. The patent at issue has the title "Therapeutic and tolerance inducing antibodies". It was granted in respect of European patent application No. 01974480.4, which originated from international patent application No. PCT/GB2001/004518, published as WO 02/30460 (hereinafter "application as filed").

Claim 1 as granted reads:

"1. A modified therapeutic antibody comprising a cell-binding antibody that includes an antibody combining site that binds to a cell-bound target antigen, said antibody being modified with a peptide that inhibits binding of the antibody to the target antigen, wherein the peptide comprises the target antigen or a domain or mimotope thereof which is reversibly bound to the antibody combining site of the antibody, said modified antibody being effective for reducing an immune response against the antibody and for producing a therapeutic effect by binding to the target antigen."

- II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Article 100(b) and (c) EPC.
- III. The opposition division held (see decision under appeal, paragraph bridging pages 3 and 4) that "claim 1 of the patent as granted does not fulfill the requirements of Article 123(2) EPC because the mimotopes referred to in the application as originally filed are characterised as

being "low affinity" mimotopes. This property of the mimotopes cannot be omitted or dissociated from the mimotopes without adding "high affinity" or "medium affinity" mimotopes to the subject-matter."

- IV. With its statement of grounds of appeal the appellant submitted a main request and auxiliary requests 1 to 5. The main request corresponds to the claims as granted.
- V. In response to the statement of grounds of appeal the opponent (hereinafter "respondent") provided arguments to the effect that the claims of the main request contained added subject-matter.
- VI. The parties were summoned to oral proceedings and a communication pursuant to Article 15(1) RPBA was issued.
- VII. Oral proceedings before the board took place on 1 October 2015. At the end of the oral proceedings the chairwoman announced the board's decision.
- VIII. The arguments of the appellant submitted in writing and during the oral proceedings may be summarised as follows:

Main request (claims as granted)

Article 100(c) EPC

Combination of features

The claimed invention related to therapeutic antibodies that were tolerogenic. The application disclosed on page 5, lines 3 to 8, that temporary blockade of the antibody combining site (ACS) of the antibody had to be for a sufficient time to induce tolerance, but once this

had been achieved the antibody should revert to or regenerate a form which could interact with the target antigen.

Subsequently, at page 5, lines 20 to 24, the application taught that one approach to modifying a therapeutic antibody was to include a compound that was reversibly bound to the ACS of the antibody. Reversible binding was further described on page 12, lines 4 to 10. As such the application as filed taught the skilled person that "temporary obstruction", "temporary blockade", "temporary blocking" and "temporary occupancy" were all equivalent expressions for describing the reversible binding of a compound to the ACS.

The description initially used the term "compound" and subsequently specified that the compound could be e.g. a peptide, see page 12, lines 4 to 6 and page 13, lines 7 to 9.

The application described on page 8 various moieties that could be used to modulate the amount of antibody that bound to the target antigen. In particular, temporary occupancy with "molecules such as the defined antigen or a domain thereof, low affinity antigenic peptides or mimotopes" was described in lines 4 to 5 and in lines 10 to 11.

The skilled person would understand that the term "defined antigen" used at lines 4 and 10 on page 8 was synonymous with the term "target antigen" used at page 5, line 23.

Basing the phrase "target antigen or a domain or mimotope thereof" in claim 1 as granted on page 8, lines 1 to 9, did not present any new information to the

skilled person.

Mimotope

In lines 4 to 5 and in lines 10 to 11 on page 8 the word "mimotope" was used without qualification. The term "low affinity" did not qualify both "antigenic peptide" and "mimotope". Such an interpretation of the phrase would be possible if the terms "antigenic peptide" and "mimotope" were synonyms and the "or" in "antigenic peptide or mimotope" was being used in a conjunctive manner. But "antigenic peptide" and "mimotope" were not synonyms. This reading was consistent with the teaching of the rest of the application, where mimotopes were not always considered as being of "low affinity". In fact the expression "low affinity mimotope" was used only once in the description, namely on page 9 in lines 15 to 16, where it was described as an alternative. Page 9 alone made it clear that the mimotope was not limited to a low affinity mimotope.

Linker

The term "mimotope" as used in claim 1 covered mimotopes with a range of affinities, and the presence of a linker did not require a limitation to low affinity mimotopes as these were disclosed in the application only in the context of an inert linker on page 9, lines 15 to 18.

Remittal to the opposition division

The case should be remitted to the opposition division for further prosecution.

IX. The arguments of the respondent submitted in writing and during the oral proceedings may be summarised as follows:

Main request (claims as granted)

Article 100(c) EPC

Combination of features

The passages on page 8, lines 4 to 5 and lines 10 to 11 of the application as filed failed to disclose the combination of features in claim 1 of a peptide that inhibited binding of the antibody to the target antigen, wherein the peptide comprised the target antigen or a domain or mimotope thereof which was reversibly bound to the antibody combining site (ACS) of the antibody.

As to the feature "reversible binding", the skilled person would derive from page 8 or page 12, lines 4 to 7 that the terms "temporary obstruction" or "temporary blockade" of the ACS were broader than "reversible binding" of a compound to the ACS. Temporary occupancy encompassed e.g. steric hindrance, see page 6, lines 20 to 23.

As to the features "peptide" or mimotope" in claim 1, the skilled person would understand, for example in view of page 8, page 12, lines 4 to 5 or page 13, lines 7 to 14, that in the application the meaning of the term "compound" was not limited to "peptide" or "mimotope"; it was broader. Hence, any disclosure in the application as filed relating to a "compound" could not be applied to "peptide" or "mimotope" because the terms were not synonymous.

Mimotope

Page 8, lines 4 to 5 and 10 to 11 referred *inter alia* to "low affinity antigenic peptides or mimotopes". The absence of a comma between "low affinity antigenic peptides" and "mimotopes" meant that these two terms had to be read in conjunction, with "low affinity" applying to both the antigenic peptides and mimotopes. Thus, the natural reading of the statements on page 8 was that the mimotope was a low affinity mimotope.

This reading was supported by the subsequent statements on page 8, lines 8 to 10 and 13 to 15, which explained that the antibody would "gradually accumulate on cell-bound or other "target" antigen if the association and dissociation constants were favourable by comparison with the "obstructive" element". The skilled person understood from this teaching that the antigenic peptide or mimotope used had to have a lower affinity for the ACS than the affinity of the cell-bound antigen for the ACS, otherwise the mimotope would bind too strongly to the ACS to be out-competed by the antigen itself.

The disclosure on page 9, lines 3 to 6 and lines 20 to 21 referred back to that on page 8, so the skilled person would read into these passages on page 9 that the mimotopes had to be low affinity mimotopes.

Linker

Claim 1 contained added subject-matter in the specific case of mimotopes attached by an inert linker to the antibody, because in the context of mimotopes attached by an inert linker only low affinity mimotopes were disclosed in the application as filed, see page 9, lines 15 to 18 in combination with page 5, lines 3 to 8 and

page 6, lines 2 to 8.

Remittal to the opposition division

The respondent did not make any submissions on this issue.

- X. The appellant requested that the decision under appeal be set aside and that the case be remitted to the opposition division for further prosecution on the basis of the main request or, alternatively, of one of the sets of claims filed as auxiliary requests 1 to 5 with the statement of grounds of appeal.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

Main request (claims as granted)

Article 100(c) EPC

1. The question to be decided in the present case is whether or not claim 1 presents the skilled person with technical information which is not directly and unambiguously derivable from the application as filed.

Combination of features

2. The application discloses on page 4, lines 5 to 7 a "modified therapeutic antibody wherein the modified therapeutic antibody as compared to the unmodified antibody has a reduced binding to its target antigen." According to page 4, lines 11 to 17 the reduced binding of the antibody to its target antigen is achieved by "a temporary obstruction of its antibody-combining site

which reduces the binding of the antibody for its natural target and wherein following administration to a host the antibody is capable of regenerating sufficient of a functionally-competent form of the therapeutic antibody to achieve the said therapeutic effect". "The temporary blockade of the antibody combining site (ACS) of the antibody must be for a sufficient time to induce tolerance within the host immune system, i.e. inhibit the immunogenic immune response against the antibody" (see page 5, lines 3 to 5). It is further disclosed on page 4, lines 24 and 25, that by "Using this antibody the immunogenicity of cell-binding antibodies may be reduced or circumvented so that antibody therapy can be used to its full potential". Once tolerance has been induced, "the antibody should revert to or regenerate a form which can interact with the therapeutic target by increasing the amount of antibody bound thereto" (see page 5, lines 6 to 8). In particular, the application discloses on page 5, lines 20 to 22, that "there is provided a therapeutic antibody that is modified to include a compound that is reversibly bound to the antibody combining site of the antibody."

3. In the board's judgement the application thus discloses to the skilled person a modified therapeutic antibody comprising a cell-binding antibody that includes an antibody combining site that binds to a cell-bound target antigen, said antibody being modified with a compound which is reversibly bound to the antibody combining site of the antibody, said modified antibody being effective for reducing an immune response against the antibody and for producing a therapeutic effect by binding to the target antigen.

4. As regards the compound which is reversibly bound to the antibody combining site of the antibody, the application teaches on page 12, lines 4 to 7 and page 13, lines 7 to 9 that this compound may be a peptide, while according to page 9, lines 20 to 21 "preferably, the native antigen, domains thereof, and peptide fragments or mimotopes are used to modify the ACS".

5. The skilled person is further taught on page 8, lines 1 to 9 of the application which particular compounds can be used in the context of the invention as follows: "The temporary blockade of the ACS (...) may be effected by the following, including;
(i) Temporary occupancy with molecules such as the defined antigen or a domain thereof, low affinity antigenic peptides or mimotopes (...)".

6. As regards the designation of one of the compounds in claim 1 by which the antibody is modified as the "target antigen" and not as the "defined antigen" as disclosed on page 8, lines 4 and 10, the board considers that the skilled person reading the application as a whole notes that while reference is made alternately to "target antigen" (e.g. on page 4, line 7; page 5, line 22; page 13, line 17), to "defined antigen" (e.g. page 8, lines 4 and 10) and to "native antigen" (page 9, line 20), these terms always define the same entity, namely the antigen against which the therapeutic antibody is directed. The technical information conveyed to the skilled person by these different terms is thus always the same. Accordingly, no new technical information is generated by using the term "target antigen" in claim 1 instead of the term "defined antigen" disclosed on page 8, lines 4 and 10.

7. Likewise, the skilled person reading the application as a whole would understand that the terms "temporary occupancy" of the ACS (used e.g. on page 8, lines 4 and 10) and "reversibly bound" to the ACS (used e.g. on page 5, line 21; page 12, line 5) convey the same technical information, namely a temporary occupancy of the ACS of the antibody which reduces the binding of the antibody for its natural target and which is reversible. This understanding is underlined by e.g. the passage on page 12, lines 4 to 10 according to which "a compound (which may be a peptide or other molecule that is capable of binding to the ACS of the antibody) is reversibly bound to the antibody binding or combining site of the antibody that is to be administered to a person. The compound occupies the binding site of the antibody for the antigen and thereby inhibits binding of the antibody to the antigen. Since the compound is reversibly bound to the antibody binding site, the antibody is capable of binding to the antigen against which the antibody is directed."

8. Accordingly, the disclosure of the various compounds on page 8, lines 4 to 5 and 10 to 11 in the context of temporary occupancy of the ACS provides a basis for the use of these compounds in the context specified in claim 1 which stipulates that the compounds are reversibly bound to the ACS.

Mimotope

9. As regards the argument, that page 8, lines 4 to 5 and 10 to 11 disclosed that the mimotopes had to be of low affinity, the board considers that the term "low affinity" in the expression "low affinity antigenic peptide and mimotopes" (see point 5 above) cannot be understood to refer to "mimotopes". This could only be

- so if the terms "antigenic peptide" and "mimotopes" were synonymous, which they are not.
10. Nor does the rest of the disclosure of the application as filed suggest any other interpretation of the expression in question. The application refers consistently to "mimotope", while the term "low affinity mimotope" is used only once in the entire application, namely on page 9, lines 15 to 18. Here, a low affinity mimotope is disclosed in the specific context of the use of an inert linker, while e.g. in the context of the use of a linker which carries an enzyme degradable motif the affinity of the mimotope is not specified as being low, see page 9, lines 3 to 6.
 11. In the board's view, the skilled person would also not have derived from the passage on page 8, lines 6 to 10, disclosing that "the antibody would gradually accumulate on cell-bound or other "target" antigen if the association and dissociation constants were favourable by comparison with the "obstructive" element", that the mimotope must be of low affinity.
 12. This is so because the application does not disclose that the mimotope has to be a low affinity mimotope in order to dissociate from the antibody. According to the application, it is only required that the binding to the ACS be reversible, which can be achieved e.g. by the use of a linker which carries an enzyme degradable motif susceptible to cleavage by host enzymes (see page 9, lines 3 to 6).
 13. The board concludes that the application as filed does not disclose - either explicitly or implicitly - that the mimotope is necessarily a low affinity mimotope.

Linker

14. The respondent further submitted that claim 1 contained added subject-matter in the specific case of mimotopes attached by an inert linker to the ACS, because in the context of mimotopes attached by an inert linker only low affinity mimotopes were disclosed in the application as filed.
15. Claim 1 does not specify that the mimotope is attached by an inert linker to the ACS, merely that it is reversibly bound to the ACS. The board has found above (see point 8), that the application as filed discloses directly and unambiguously a mimotope which is reversibly bound to the ACS of the antibody. Therefore, respondent's argument is without merit.

Conclusion

16. In the board's judgement, the application as a whole in combination with the passage on page 8, lines 1 to 9 discloses a modified therapeutic antibody having all the features of the antibody of claim 1.
17. For the reasons indicated above the board decides that claim 1 of the main request does not contain subject-matter which extends beyond the content of the application as filed (Article 100(c) EPC). The appeal is thus allowable.

Remittal to the opposition division

18. The decision under appeal was based only on one of the grounds of opposition relied on by the respondent, namely that the subject-matter of the European patent extended beyond the content of the application as filed

(Article 100(c) EPC). The opposition division did not decide on the other grounds of opposition put forward - lack of novelty, lack of inventive step and insufficiency of disclosure (see section II above).

19. Under Article 111(1) EPC, following the examination as to the allowability of the appeal, the board decides on the appeal, and in doing so may either exercise any power within the competence of the department which was responsible for the decision appealed or remit the case for further prosecution.

20. In a case such as the present one, where the opposition division has dealt with only one of the grounds of opposition, the board considers it appropriate to exercise its discretion under Article 111(1) EPC to remit the case to the opposition division for further prosecution, thereby giving the parties the possibility of having their case heard by two instances.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the opposition division for further prosecution on the basis of the claims of the main request (patent as granted).

The Registrar:

The Chairwoman:



D. Hampe

G. Alt

Decision electronically authenticated