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**Datasheet for the decision
of 12 December 2017**

Case Number: T 1136/13 - 3.3.04

Application Number: 03786140.8

Publication Number: 1581559

IPC: C07K16/00, C07K16/40, C07K16/24

Language of the proceedings: EN

Title of invention:
VL dAb FC fusion

Patent Proprietor:
Domantis Limited

Opponent:
Fisher, Adrian J.

Headword:
Single variable domain fusion protein/DOMANTIS

Relevant legal provisions:
EPC Art. 56
EPC R. 115(2)
RPBA Art. 15(3)

Keyword:
All claim requests - inventive step (no)

Decisions cited:

Catchword:



Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 1136/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 12 December 2017

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
7 March 2013 concerning maintenance of the
European Patent No. 1581559 in amended form.**

Composition of the Board:

Chairwoman G. Alt
Members: M. Montrone
M. Blasi

Summary of Facts and Submissions

- I. An appeal was lodged by the opponent (hereinafter "appellant") against the interlocutory decision of the opposition division concerning maintenance of European patent No. 1 581 559. The patent is based on European application No. 03 786 140.8, which was filed as international application published as WO 2004/058820 (hereinafter "the application as filed"). The patent has the title "*V_L dAb Fc fusion*".
- II. The opposition division held in the decision under appeal that the amended main request met the requirements of the EPC.
- III. The appellant submitted with the statement of grounds of appeal arguments why the subject-matter of the main request *inter alia* lacked an inventive step in view of the teaching of document D7 as the closest prior art document combined with either the teaching in document D20 or the teaching in one of the newly submitted documents D30 to D33 (see section VI below). The admission of these new documents was requested.
- IV. In reply to the statement of grounds of appeal, the patent proprietor (hereinafter "respondent") submitted a main request which was identical to the main request dealt with in the decision under appeal and sets of claims of three auxiliary requests. The respondent *inter alia* requested that documents D30 to D33 not be admitted into the appeal proceedings and, should document D32 be admitted, that the case be remitted to the opposition division for further prosecution.

Claim 17 of the main request reads:

"17. A dAb-effector group suitable for *in vivo* use which comprises an antibody single variable domain having an epitope binding specificity attached to one or more antibody constant regions selected from the group consisting of: an antibody CH1 heavy chain domain, an antibody CH2 heavy chain domain, an antibody CH3 heavy chain domain, and a hinge region of an antibody molecule; wherein the antibody single variable domain is a light chain variable domain."

Claim 17 of auxiliary request 1 reads:

"17. A dAb-effector group suitable for *in vivo* use which comprises an antibody single variable domain having an epitope binding specificity attached to an effector group comprising the constant region domain CH2 and/or CH3; wherein the antibody single variable domain is a light chain variable domain."

Claim 17 of auxiliary request 2 differs from claim 17 of the main request in that the feature "and further wherein the dAb-effector group is a single chain molecule" has been added at the end.

Claim 17 of auxiliary request 3 differs from claim 17 of auxiliary request 1 in that the feature "and further wherein the dAb-effector group is a single chain molecule" has been added at the end.

- V. The parties were informed of the board's preliminary view in a communication pursuant to Article 15(1) RPBA. The board indicated *inter alia* that it considered that the subject-matter of the main request lacked an

inventive step in view of the teaching of document D7 combined with that of document D20.

VI. The following documents are cited in this decision:

D7: Powers D.B. *et al.*, 2001, *J. Immunol. Meth.*, 251: 123-135.

D17: Leitzgen K. *et al.*, 1997, *J. Biol. Chem.*, 272: 3117-3123.

D20: van den Beucken T. *et al.*, 2001, *J. Mol. Biol.*, 310: 591-601.

D21: Wu T.T., 2001, *Analytical Molecular Biology*, Kluwer Academic Publishers, 18

The bibliographic data of documents D30 to D33 are not indicated here, since they are not required for the purposes of the decision (see point 2 of the reasons below).

VII. Oral proceedings before the board were held on 12 December 2017, in the absence - as announced - of the duly summoned respondent. At the end of the oral proceedings the chairwoman announced the board's decision.

VIII. The appellant's arguments, as far as they are relevant for the decision, may be summarised as follows:

Inventive step (Article 56 EPC)

Main request - claim 17

Document D7 represented the closest prior art for the subject-matter of claim 17. The document disclosed a fusion protein between a single-chain variable domain antibody fragment (scFv) and the constant part of an immunoglobulin (Fc) molecule, i.e. a so-called scFv-Fc fusion protein. The Fc part was added for increasing the half-life of the scFv part of the construct.

The subject-matter of claim 17 differed from the scFv-Fc fusion protein in that the claimed fusion protein comprised a single light chain variable (V_L) domain as antigen binding molecule instead of an scFv molecule. A particular technical effect was not associated with this difference.

The technical problem was thus the provision of an alternative to the scFv-Fc fusion protein disclosed in document D7.

The replacement of an scFv molecule by a single V_L domain was obvious for the skilled person looking for an alternative antigen binding molecule, since both molecules were known to bind to antigens on their own, as for example disclosed in document D20. Furthermore, document D20 stated explicitly that "*The simpler architecture of these single domain molecules makes them attractive alternatives to scFv antibodies*" (see page 599, column 1, lines 12 to 15).

IX. The respondent's arguments, as far as they are relevant for the decision, may be summarised as follows:

Inventive step (Article 56 EPC)

Main request - claim 17

The scFv-Fc fusion protein as disclosed in document D7 represented the closest prior art.

The claimed invention differed from the scFv-Fc construct in document D7 in that, for antigen binding, a single V_L domain, and not a scFv molecule, was attached to the effector Fc group.

The objective technical problem was the provision of an alternative antigen binding construct comprising an Fc effector group.

The replacement of an scFv molecule by a single V_L domain was not obvious for the skilled person starting from the scFv-Fc fusion protein disclosed in document D7. This was so because document D17 itself described scFv molecules as "*One of the most useful antibody fragments*" for antigen binding without suggesting alternatives having the same function (see page 124, column 1, first paragraph). Therefore, the skilled person had no motivation to replace the scFv molecule by a single V_L domain.

Assuming that the skilled person was motivated to look for alternatives, the selection of a single V_L domain was not obvious. The skilled person was aware that the decisive complementarity determining region (CDR) for antigen binding was CDRH3, i.e. the CDR3 region of the heavy chain variable (V_H) domain. This was supported by

the statement in document D21 which reads "*if we want to design an antibody with a special property, we should start from selecting a CDRH3*" (see page 18).

Thus, the skilled person would have rather selected a single V_H domain than a single V_L domain as an alternative to an scFv molecule. Any other conclusion was based on hindsight.

The subject-matter of claim 17 was also not obvious in view of the teachings of document D7 combined with document D20. Firstly, as set out above, the skilled person was aware of the significance of the CDRH3 region for a specific antigen binding. Thus, he would not have turned to the single V_L domain reported in document D20 without hindsight.

Secondly, document D20 disclosed the construction of a V_L domain library for evaluating the use of single V_L domains as new immunomodulatory molecules. However, the document mentioned in its "*Discussion*" section solely applications for single V_L domains that relied on the exploitation of their small size. The document reported in this context that "*Their small size means that they may be more suitable for in vivo imaging applications than whole antibodies or Fabs, and also possible for gene therapy vector retargeting where there is a size restriction on the binding ligand displayed on the viral surface*" (see page 599, column 1, lines 7 to 12).

Likewise, document D20 stated that "*The simpler architecture of these single domain molecules makes them attractive alternatives to scFv antibodies for intracellular targeting applications*" (see page 599, first column, lines 12 to 15). Thus, the skilled person, in view of the advantage of the small size of

the V_L domain for intracellular targeting applications, would not have replaced the scFv molecule by a V_L domain in the scFv-Fc fusion protein disclosed in document D7, since the resulting V_L-Fc construct would effectively be larger than the V_L domain alone.

- X. The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

The respondent requested in writing that the appeal be dismissed, i.e. that the patent be maintained in the form considered allowable by the opposition division, or alternatively, that the patent be maintained on the basis of the claims of one of auxiliary requests 1 to 3, all filed in reply to the appellant's statement of grounds of appeal. Furthermore, the respondent requested that documents D30 to D33 not be considered in the appeal proceedings, and, were document D32 to be admitted, that the case be remitted to the opposition division.

Reasons for the Decision

1. The duly summoned respondent did not attend the oral proceedings, which in accordance with Rule 115(2) EPC took place in its absence. By not attending the oral proceedings, the respondent relinquished the opportunity to present its comments. In accordance with Article 15(3) RPBA, the respondent was treated as relying on its written case.
2. None of the parties relied upon documents D30 to D33 in their submissions relating to the aspects of patentability decided by the board in this decision,

nor has the board considered the content of any of these documents in reaching its decision. Therefore, the requests in relation to documents D30 to D33 (see section X above) did not need to be decided on.

Introduction to the invention

3. The invention concerns engineered, so-called single domain-effector-group immunoglobulins, i.e. "dAb-effector group" constructs, comprising a single variable domain of an antibody having an antigen or epitope binding specificity, i.e. the "dAb" group, and one or more constant regions and/or a hinge region of an antibody, i.e. the "effector" group (see e.g. paragraph [0023] of the patent).
4. The "Fc" part of an IgG antibody comprises the constant regions derived from the second and third constant domains (CH2 and CH3) of the antibody's two heavy chains, including the hinge region (see e.g. document D7, page 124, column 2, first paragraph).
5. The effector group extends the half-life of the construct *in vivo*, which increases the therapeutic availability of the single variable domains compared with single variable domains without the effector group (see e.g. paragraph [0034] of the patent).
6. The single variable domain can be derived either from the heavy chain (V_H) or from the light chain (V_L) of an antibody, both of which are able to bind on their own to antigens (see paragraphs [0002], [0006] and [0024] of the patent).

Claim construction - claim 17

7. Claim 17 is directed to dAb-effector group constructs comprising, as the dAb group, a single V_L domain of an antibody having an epitope binding specificity and, as the effector group, one or more antibody constant regions selected from the group consisting of the heavy chain constant domains C_{H1} , C_{H2} , C_{H3} , and a hinge region of an antibody molecule.
8. The claim is therefore directed to several alternative dAb-effector group constructs, including one construct comprising a single V_L domain bound to an effector group consisting of a hinge region and the two heavy chain domains C_{H2} and C_{H3} . This embodiment of claim 17 will be considered in the following and will hereinafter be referred to as the " V_L -Fc construct".

Inventive step (Article 56 EPC) - claim 17

Closest prior art

9. The board agrees with the parties that document D7 represents the closest prior art for the V_L -Fc construct as an embodiment of claim 17.
10. Document D7 discloses antigen binding constructs, comprising a monovalent single-chain variable antibody fragments (scFv) part and an Fc part, so-called "*scFv-Fc*" constructs (see page 124, column 1, first and third paragraph and column 2, first paragraph). The scFv part of the construct consists of a single V_H domain and a single V_L domain of an antibody joined by a short peptide linker. They are fused to an Fc region derived from a human IgG1 antibody consisting of the hinge and the C_{H2} and C_{H3} constant domains. The scFv molecule is

the antigen-binding part in this construct. The Fc region is attached to increase the serum half-life of the construct and hence its effector part.

Technical problem and solution

11. The V_L -Fc construct considered here differs from the scFv-Fc construct disclosed in document D7 in that the scFv molecule is replaced by a single V_L domain.
12. The board agrees with the parties that there is no advantageous technical effect associated with this difference, since both the scFv molecule and the single V_L domain bind on their own to antigens. Thus, the objective technical problem to be solved is the provision of an alternative molecule binding to antigens in a construct comprising an Fc molecule as effector group.
13. The V_L -Fc construct as embodiment of claim 17 solves this problem in view of the two exemplary V_L -Fc proteins disclosed in examples 4 and 5 of the patent.

Obviousness

14. In view of the parties' submissions it has to be assessed in the present case whether or not the skilled person, starting from the scFv-Fc construct disclosed in document D7 and faced with the technical problem defined above, would replace the scFv molecule in the construct by a single V_L domain in the light of the teaching of document D7 alone or in the light of the combined teachings of documents D7 and D20, so as to arrive at the V_L -Fc construct referred to in claim 17 in an obvious manner.

15. It is common ground between the parties that document D7 does not suggest or hint at alternatives of the scFv molecule for antigen binding. Thus, the board concludes that the V_L-Fc construct referred to in claim 17 cannot be considered as obvious in the light of the teaching of document D7 alone.
16. With regard to the combination of documents D7 and D20, document D20 discloses various single V_L domains and their ability to bind on their own to B7.1 or B7.2 antigens (see abstract). The document reports in the context of binding that "*All selected VL domains bind with a high degree of specificity to their target antigen and, at least for the clones binding to either B7.1 or B7.2, binding appears to be mediated as expected through the CDR loops. Indeed, upon affinity maturing the B7.1-specific clone B10503, we were able to recover improved affinity variants, which had mutations in both the CDR1 and CDR3 loops" (see page 598, column 2, second paragraph, emphasis added).*

Furthermore, the authors of document D20 report on page 599 that "*We foresee a number of applications for human single VL domains. These include more easy engineering into multivalent and multispecific molecules than regular antigen combining sites derived from two domains.³⁰ Their small size means that they may be more suitable for in vivo imaging applications than whole antibodies or Fabs,^{34,35} and also possibly for gene therapy vector retargeting where there is a size restriction on the binding ligand displayed on the viral surface.³⁶ The simpler architecture of these single domain molecules makes them attractive alternatives to scFv antibodies for intracellular targeting applications" (see page 599, column 1, second paragraph, emphasis added).*

17. In the board's view, the skilled person would derive from the passages in document D20 set out above: firstly, that the single V_L domains bind on their own with high specificity and affinity to antigens and that the complementarity determining regions of these variable light chains (CDRLs), including CDRL3, are decisive and sufficient for this function; secondly, that the single V_L domains, due to their independent binding properties, can be more easily engineered into multivalent and/or multispecific molecules, since the binding sites from the CDRs of the variable heavy chain are not required; and thirdly, that the simpler structure of the single V_L domains, including their small size, makes them attractive alternatives to scFv molecules for *in vivo* targeting applications.

18. The respondent submitted that the skilled person would not have considered the replacement of scFv molecules in the scFv-Fc construct disclosed in document D7 by single V_L domains as alternatives in the light of the teaching of document D20. This was so because (i) the skilled person was aware that the CDR3 region of the V_H domain was decisive for the antigen binding specificity, and (ii) all of the suggested *in vivo* applications relied on the small size of the V_L domains. However, their small size would be lost when replacing the scFv molecule by a single V_L domain in the construct disclosed in document D20, since a V_L -Fc construct was larger than the single V_L domain.

- 18.1 The board is not convinced by these arguments, for the following reasons. As set out in point 16 above, document D20 reports that single V_L domains bind their antigens with a "*high degree of specificity*". Thus, the skilled person is taught by document D20 that the CDRs from the variable light chain are sufficient for a

specific binding, i.e. that the CDRH3 region is not necessary. Hence, in the light of document D20 the skilled person has no reason to prefer single V_H domains over single V_L domains or to disregard the latter domains when looking for alternative molecules suitable for specifically binding to antigens.

18.2 Furthermore, although document D20 underlines the advantages of the small size of single V_L domains for *in vivo* applications, in the board's view, the skilled person would not have been discouraged from engineering them into larger molecules by this disclosure, for the following reasons. Firstly, document D20 itself suggests that single V_L domains might be used for the "*engineering into multivalent and multispecific molecules*" (see point 16 above), i.e. constructs that are larger than single V_L domains, due to the presence of more than one antigen binding domain.

18.3 Secondly, the document suggests in the same paragraph on page 599 (see point 16 above) that "*The simpler architecture of these single domain molecules makes them attractive alternatives to scFv antibodies for intracellular targeting applications*".

In the board's view, the skilled person would derive from the term "*simpler architecture*" that V_L domains have a simpler structure compared to scFv molecules, i.e. one antigen binding domain instead of two, including a linker molecule (see point 10 above). Thus, although the simpler structure of the single V_L domains is also associated with a smaller size compared to scFv molecules due to a reduced number of functional units, it is rather the structural aspect which makes them attractive as alternatives to scFv molecules. Thus, contrary to the appellant's view, this passage in

document D20 cannot be understood as a suggestion to avoid the use of single V_L domains in the construction of fusion proteins, if desired.

19. The board therefore concludes that the replacement of scFv molecules by single V_L domains in the scFv-Fc construct disclosed in document D7 is obvious for the skilled person. Thus, the subject-matter of claim 17, and as a consequence thereof the main request, does not meet the requirements of Article 56 EPC.

Auxiliary requests 1 to 3 - claims 17

20. The subject-matter of claim 17 of auxiliary request 1 differs from claim 17 of the main request in that the features "one or more antibody constant regions selected from the group consisting of: an antibody CH1 heavy chain domain, an antibody CH2 heavy chain domain, an antibody CH3 heavy chain domain, and a hinge region of an antibody molecule" have been replaced by the features "an effector group comprising the constant region domain CH2 and/or CH3", i.e. the number of alternatives to form the antibody constant regions has been reduced.

Claim 17 of auxiliary request 2 and 3 differs from claim 17 of the main request in that the feature "and further wherein the dAb-effector group is a single chain molecule" has been added, meaning that the two parts of the dAb-effector group construct are linked.

21. Claim 17 of all three auxiliary requests is therefore directed to dAb-effector group constructs, *inter alia* one consisting of a single V_L domain bound to an effector molecule consisting of the hinge region and

the two heavy chain domains C_{H2} and C_{H3}, this being the V_L-Fc construct considered above in relation to the main request (see point 6). The conclusions of the board with regard to lack of an inventive step of the subject-matter of claim 17 of the main request therefore apply *mutatis mutandis* to claim 17 of auxiliary requests 1 to 3, which therefore does not meet the requirements of Article 56 EPC either.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated