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Language of the proceedings: EN

Title of invention:
Dual-specific ligand and its use

Patent Proprietor:
Domantis Limited

Opponent:
Fisher, Adrian J.

Headword:
Dual-specific ligand/DOMANTIS

Relevant legal provisions:
EPC Art. 54
EPC R. 115(2)
RPBA Art. 12(4), 15(3)

Keyword:
Novelty of all requests - (no)
Requests could have been filed in first instance proceedings - (yes)

Decisions cited:

Catchword:

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Beschwerdekammern

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Case Number: T 1645/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 27 March 2018

Appellant: (Patent Proprietor)	Domantis Limited 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Respondent: (Opponent)	Fisher, Adrian J. c/o Carpmaels & Ransford One Southampton Row London WC1B 5HA (GB)
Representative:	Goodfellow, Hugh Robin Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 10 May 2013 revoking European patent No. 1399484 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman	G. Alt
Members:	M. Montrone
	L. Bühler

Summary of Facts and Submissions

I. An appeal was lodged by the patent proprietor (hereinafter "appellant") against the decision of the opposition division to revoke European patent No. 1 399 484. The patent is based on European application No. 02 748 987.1, which was filed as an international application and published as WO 03/02609 with the title "*Dual-specific ligand and its use*".

II. In the decision under appeal the opposition division held that claim 1 of the main request comprised subject-matter extending beyond the content of the application as filed and that the subject-matter of claims 1 of auxiliary requests 1 to 4 lacked an inventive step in view of the disclosure of document D2 (WO 90/05144).

III. With its statement of grounds of appeal the appellant submitted a main request and nine auxiliary requests. The main request and auxiliary requests 1, 4, 5 and 9 in the present appeal proceedings correspond to the main request and auxiliary requests 1 to 4 respectively as dealt with in the decision under appeal, while auxiliary requests 2, 3 and 6 to 8 were new, i.e. filed for the first time in the appeal proceedings.

Claims 1 of the main request and of auxiliary request 5 read as follows:

"1. A dual-specific ligand comprising an immunoglobulin heavy chain single variable domain having a binding specificity to a first antigen or epitope and a complementary immunoglobulin light chain single variable domain having a binding specificity to a second antigen or epitope, wherein said domains do not

share the same specificity, and wherein the variable domains bind their respective antigens or epitopes simultaneously".

The subject-matter of claims 1 of auxiliary requests 1 and 6 differs from claim 1 of the main request in that the feature "wherein said domains do not share the same specificity" has been replaced by the feature "wherein said first and second domains lack complementary domains which share the same specificity".

The subject-matter of claims 1 of auxiliary requests 4 and 9 differs from claim 1 of the main request in that the feature "and wherein the V_H and V_L are not provided as an antibody Fab region" has been added.

IV. With its reply to the appellant's statement of grounds of appeal the opponent (hereinafter "respondent") submitted arguments as to why the main request *inter alia* lacked an inventive step in view of the teaching of document D2 and why auxiliary requests 2, 3, 7 and 8 should not be admitted into the appeal proceedings.

V. The parties were summoned to oral proceedings and later, in a communication pursuant to Article 15(1) RPBA, were informed of the board's preliminary view. The board indicated *inter alia* that, in view of the respondent's submissions on the lack of an inventive step in the subject-matter of claim 1 of the main request in view of the disclosure of document D2, the subject-matter of claim 1 of the main request appeared to lack novelty (Article 54 EPC).

VI. In reply the appellant announced that it would not attend the oral proceedings but maintained the requests set out in its statement of grounds of appeal. It did

not comment on issues in the respondent's submission or the board's communication.

VII. Oral proceedings before the board were held on 27 March 2018, in the absence - as announced - of the appellant. At the end of the oral proceedings the chairwoman announced the board's decision.

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

Novelty (Article 54 EPC)

Main request

At the oral proceedings, the respondent shared the view expressed by the board in its communication pursuant to Article 15(1) RPBA that the subject-matter of claim 1 lacked novelty in view of the disclosure of document D2.

Admission of auxiliary requests 2, 3, 7 and 8 (Article 12(4) RPBA)

Auxiliary requests 2, 3, 7 and 8 should not be admitted into the appeal proceedings, since the opportunity to file amended claim requests had been explicitly offered to the appellant during the oral proceedings before the opposition division but refused (see minutes, points 46 and 49).

IX. The appellant had requested in writing that the decision under appeal be set aside and that the patent be maintained on the basis of the set of claims of the main request or, alternatively, of one of auxiliary

requests 1 to 9, all filed with its statement of grounds of appeal.

The respondent requested that the appeal be dismissed. It further requested that auxiliary requests 2, 3, 7 and 8 not be admitted into the appeal proceedings.

Reasons for the Decision

1. The duly summoned appellant did not attend the oral proceedings, which in accordance with Rule 115(2) EPC and Article 15(3) RPBA took place in its absence.

2. The board in its communication pursuant to Article 15(1) RPBA expressed a reasoned provisional opinion on the issues to be discussed at the oral proceedings, which included the issue of novelty for the subject-matter of claim 1 of the main request vis-à-vis the disclosure of document D2. Thus, the grounds given by the board in the present decision with regard to novelty were known to the appellant from the board's communication. Furthermore, the appellant was given the opportunity to make written and/or oral submissions in respect of the grounds and evidence on which the present decision is based. However, the appellant neither replied to the board's communication nor attended the oral proceedings. In these circumstances, the board considers that the the right to be heard (Article 113(1) EPC) has been respected.

3. The invention concerns engineered, so-called "*dual-specific ligand*" constructs comprising complementary immunoglobulin-derived single variable heavy chain (V_H) and light chain (V_L) domains, wherein each domain binds

to a different antigen or epitope (see e.g. paragraph [0009] of the patent).

4. The term "*complementary*" recited in claim 1 is construed to relate to the presence of a single V_H domain and a single V_L domain together in a ligand construct which "*do not bind a target molecule co-operatively, but act independently on different target epitopes which may be on the same or different molecules*" (see paragraphs [0010] and [0042] of the patent). In other words, both single domains bind on their own, i.e. independently, to different antigens/ epitopes.

5. Furthermore, the term "*dual-specific ligand*" in claim 1 is understood to relate to a combination of V_H/V_L domains in a pair, wherein each pair has two different binding specificities (see paragraph [0009] of the patent).

Novelty (Article 54 EPC)

Main request

6. Claim 1 is directed to a dual-specific ligand comprising an immunoglobulin heavy chain single variable domain having a binding specificity for a first antigen and a complementary light chain single variable domain having a binding specificity for a second antigen, wherein both domains do not share the same binding specificity and bind their respective antigens simultaneously.

7. Thus, the claim is directed to several alternative dual-specific ligands, including a construct consisting

of a dimer of a single V_H domain linked to a single V_L domain (hereinafter a "V_H/V_L" construct), wherein each domain binds to a different antigen/epitope, or in other words, each domain has a different binding specificity. This embodiment of claim 1 will be considered in the following.

8. Document D2 discloses single domain ligands derived from immunoglobulins including so-called "*receptors*" comprising these ligands (see title, page 1, lines 5 to 9). The document discloses as a "*first aspect*" isolated immunoglobulin-derived molecules having "*a single domain ligand consisting at least part of the variable domain of one chain of a molecule from the Ig superfamily. Preferably, the ligand consists of the variable domain of an Ig light, or, most preferably, heavy chain*" (see page 6, lines 17 to 23, emphasis added). In other words, document D2 discloses as a first aspect of the invention isolated single immunoglobulin-derived ligand molecules consisting of either single V_H or V_L domains.

8.1 Furthermore, document D2 discloses engineered "*receptor*" constructs of the single domain ligand molecules comprising *"a ligand according to the first aspect of the invention linked to one or more of an effector molecule, a label, a surface, or one or more other ligands having the same or different specificity*" (see page 8, lines 8 to 12, emphasis added).

8.2 In the board's view, the skilled person would derive from the passage cited in point 8.1 above that all of the disclosed receptor constructs comprise a "*ligand according to the first aspect of the invention*", i.e. a single V_H or V_L domain (see point 8 above) that are

linked to other molecules including at least one other ligand, i.e. one further single V_H or V_L domain. In other words, a dimer or pair of single V_H and/or V_L domain units in all possible combinations, having either the same or a different antigen/epitope binding specificity. Thus, document D2 explicitly discloses six different engineered dimeric constructs, i.e. three V_H/V_L, V_H/V_H or V_L/V_L constructs, wherein each of the three constructs has either the same or a different antigen binding specificity.

8.3 Therefore, document D2 discloses a V_H/V_L construct having different binding specificities as one of six constructs that is detrimental to the novelty of the embodiment of claim 1 under consideration (see point 7 above).

8.4 The board's finding in point 8.3 above is further corroborated by several examples of receptor constructs in document D2 that comprise at least one dimer of V_H and/or V_L domains having different binding specificities. For example, page 9, lines 11 to 14, reads: "*Receptors comprising at least two ligands can be used, for instance, in diagnostic tests. The first ligand will bind to a test antigen and the second ligand will bind to a reporter molecule*" (emphasis added). Furthermore, page 9, lines 18 to 25, discloses that "*Alternatively, such receptors may be useful in increasing the binding to an antigen. The first ligand will bind to a first epitope of the antigen and the second ligand will bind to a second epitope. Such receptors may also be used for increasing the affinity and specificity of binding to different antigens in close proximity on the surface of cells. The first ligand will bind to the first antigen and the second epitope to the second antigen*" (emphasis added).

8.5 Furthermore, example 11 in document D2 reports on the "*Coexpression of VH domains with Vk repertoire*" (see heading; remark added by the board: the term "*Vk*" is the abbreviation of Vkappa, i.e. an immunoglobulin light chain variable domain), allowing the generation of engineered constructs comprising single V_H and V_L domains binding to different epitopes. The example specifies as a first step in achieving this goal that: "*A repertoire of VAC genes was derived by PCR using primers as <'> described in Example 2 from DNA prepared from mouse spleen and also from mouse spleen mRNA using the primers VK3FOR and VK2BACK and a cycle of 94°C for 1 min, 60°C for 1 min, 72°C for 2 min*" (see page 61, lines 32 to 36). In the board's view, the skilled person would derive from this disclosure that specific primers in a PCR-based approach are used to amplify a repertoire of rearranged genomic genes encoding variable immunoglobulin kappa light chain domains, i.e. a library of V_{Lkappa} domains.

With regard to the second step, example 11 discloses that: *"The PCR amplified DNA was fractionated on the agarose gel, the band excised and cloned into a vector which carries the VHLYS domain (from the D1.3 antibody)* (i.e. a specific single V_H domain binding to lysozyme ("*LYS*"), remark added by the board)*, and a cloning site (Sad and Xhol) for cloning of the light chain variable domains with a myc tail (pSWIVHLYS-VKPOLYMYC, Figure 22)*" (see page 61, line 36, to page 62, line 3). This process allows the expression of ligand constructs comprising the specific single V_{HLYS} domain linked to a library of different single V_{Lkappa} domains.

Example 11 further reports as the third step on a screening procedure for identifying constructs consisting of single V_{HLYS}/V_{Lkappa} domain units binding

to lysozyme, which is described as follows (see page 62, lines 5 to 15, emphasis added):

"*Clones were screened for lysozyme binding activities as described in Examples 5 and 7 via the myc tag on the light chain variable domain, as this should permit the following kinds of VK domains to be identified:*
(1) those which bind to lysozyme in the absence of the VHLYS domain;
(2) [...]
(3) [...]".

In the board's opinion, the skilled person would derive from the passage above that screening allows the identification of single V_{Lkappa} domains that bind independently of the V_{HLYS} domain to epitopes of lysozyme, or in other words V_{Lkappa} domains that bind to different epitopes of lysozyme than the V_{HLYS} domain.

9. Thus in the passages cited above, document D2 discloses dimeric ligand constructs consisting of single V_H/V_L domains having different antigen/epitope binding specificities, i.e. the considered embodiment of claim 1 (see point 7 above).

10. Therefore the board concludes that the subject-matter of claim 1 is not novel and that the main request does not meet the requirements of Article 54 EPC.

Auxiliary requests 1, 4 to 6 and 9 - claim 1

11. The subject-matter of claims 1 of auxiliary requests 1 and 6 differs from claim 1 of the main request in that the feature "wherein said domains do not share the same specificity" has been replaced by the feature "wherein

said first and second domains lack complementary domains which share the same specificity".

12. The subject-matter of claims 1 of auxiliary requests 4 and 9 differs from claim 1 of the main request in that the feature "and wherein the V_H and V_L are not provided as an antibody Fab region" has been added. In other words, this amendment excludes Fab-derived V_H/V_L constructs. The board construes this disclaimer to be directed to the exclusion of constant regions of the immunoglobulin molecule in the claimed dual-specific ligands, which in a Fab molecule normally link the variable domains of the heavy and light chains.

13. The subject-matter of claim 1 of auxiliary request 5 is identical to that of the main request.

14. The board notes that all of the amended claims 1 of auxiliary requests 1, 4, 6 and 9 still encompass as an embodiment the V_H/V_L construct of claim 1 of the main request considered above. Furthermore, document D2 discloses that: "*Alternatively the heavy and light chain variable domains are covalently linked together with a peptide, as in the single chain antibodies, or peptide sequences attached, preferably at the C-terminal end which will associate through forming cysteine bonds or through non-covalent interactions, such as the introduction of "leucine zipper" motifs. However, in order to isolate pairs of tightly associated variable domains, the Fv fragments are preferably* used" (see page 26, lines 1 to 8, emphasis added). Therefore, document D2 discloses several options for linking single variable domains in the disclosed engineered receptor constructs that all do not rely on constant regions of immunoglobulin molecules, for example peptides as in single chain

antibodies. In other words, the disclosed V_H/V_L constructs in document D2 are "not provided as an antibody Fab region" (see point 12 above).

15. Thus, either for the reasons set out above for the subject-matter of claim 1 of the main request (auxiliary requests 1, 5 and 6) or for those reasons in combination with the arguments in point 14 above (auxiliary requests 4 and 9), the subject-matter of claims 1 of auxiliary requests 1, 4 to 6 and 9 lacks novelty in view of the disclosure in document D2. Thus, none of these requests meets the requirements of Article 54 EPC.

Admission of auxiliary requests 2, 3, 7 and 8 (Article 12(4) RPBA)

16. Auxiliary requests 2, 3, 7 and 8 were all filed for the first time by the appellant with its statement of grounds of appeal. According to Article 12(1) and (2) RPBA, these requests are part of the appeal proceedings. The board, however, pursuant to Article 12(4) RPBA, has a discretion to hold inadmissible facts, evidence or requests which could have been presented in the first instance proceedings.

17. According to the appellant, auxiliary request 2 has essentially been amended in claim 1 to specify that the use of complementary domains allows the two domain surfaces to pack together, to be sequestered from the solvent, and to stabilise each other. Furthermore, minor amendments for the correction of scanning errors have been introduced in claims 2, 7, 8 and 15. The appellant further submitted that auxiliary request 3 was the combination of the amendments made in auxiliary

requests 1 and 2, while auxiliary requests 7 and 8 were the combination of the amendments made in auxiliary requests 2 and 5, or 3 and 5, respectively (see statement of grounds, item D, point 1, and items E, I, J, respectively).

18. Thus, since the amendments in auxiliary request 2 are likewise contained in the other three requests, auxiliary requests 2, 3, 7 and 8 all comprise subject-matter which was never presented in the first instance proceedings. Furthermore, the appellant gave no reasons why these requests could not have been submitted during the opposition proceedings.

19. Therefore, the admission of auxiliary requests 2, 3, 7 and 8 into the appeal proceedings hinges on whether the appellant was in a position to make its submissions earlier, and whether it could have been expected to do so in the circumstances of the present case.

20. Points 46 and 49 of the minutes of the oral proceedings before the opposition division show that the appellant did explicitly refrain from submitting further amended claim requests, despite having the opportunity to do so, after it had been informed by the chairman of the opposition division that the ligands according to claim 1 of auxiliary request 1 lacked an inventive step since they were not limited to ligands having the recited advantages. Moreover, it is derivable from page 8, point 37, sixth paragraph, of the minutes that in the appellant's view these advantages were *inter alia* that: "*The maintenance of the complementarity has a purpose, which is evident from §9 line 34; §8 p 4 line 14; §10, column line 48, resulting in that VH and VL stabilize each other creating a molecule that binds two different antigens and that does not have the undesirable*

problems characteristic of bi-specific antibodies" (cited references are to paragraphs in the patent; remark and emphasis added by the board).

21. In this context, the board notes that the passage indicated in paragraph [0010], line 48, of the patent cited by the appellant reads as follows: "*The inventors have found that the use of complementary variable domains allows the two domain surfaces to pack together and be sequestered from the solvent. Furthermore the complementary domains are able to stabilise each other*", i.e. it relates to the features that are now recited in claims 1 of auxiliary requests 2, 3, 7 and 8.

22. Accordingly, on the basis of the evidence on file, in the board's opinion the appellant was already explicitly given the opportunity to file amended auxiliary requests 2, 3, 7 and 8 during the first-instance proceedings but did not avail itself of this option. Furthermore, the appellant has not submitted reasons why it now seeks to introduce these requests into the appeal proceedings.

23. In view of the above considerations, the board decided not to admit auxiliary requests 2, 3, 7 and 8 into the appeal proceedings (Article 12(4) RPBA).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated