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Datasheet for the decision of 6 October 2016

Case Number: T 2159/12 - 3.3.04

Application Number: 04739378.0

Publication Number: 1629012

IPC: C07K16/28, A61K39/395, A61P35/00, A61P35/02, A61P19/02

Language of the proceedings: EN

Title of invention:
Pharmaceutical compositions comprising bispecific anti-CD3, anti-CD19 antibody constructs for the treatment of B-cell related disorders

Applicant:
Amgen Research (Munich) GmbH

Headword:
Bispecific antibody/AMGEN

Relevant legal provisions:
EPC Art. 56, 111(1), 123(2)
RPBA Art. 13(1)

Keyword:
Amendments - allowable (yes)
Inventive Step - main request - claim 1 (yes)
Remittal to the department of first instance - (yes)

Decisions cited:

Catchword:

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Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 2159/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 6 October 2016

Appellant: (Applicant)	Amgen Research (Munich) GmbH Staffelseestrasse 2 81477 München (DE)
Representative:	Schiweck, Weinzierl & Koch European Patent Attorneys Landsberger Straße 98 80339 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 26 April 2012 refusing European patent application No. 04739378.0 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	A. Chakravarty
	M. Blasi

Summary of Facts and Submissions

I. Appeal lies from the decision of the examining division to refuse the European patent application No. 04739378.0, entitled "*Pharmaceutical compositions comprising bispecific anti-CD3, anti-CD19 antibody constructs for the treatment of B-cell related disorders*".

II. The examining division considered a main request and an auxiliary request and held that the subject-matter of claim 1 of both lacked inventive step.

III. With the statement of grounds of appeal the appellant submitted a main and two auxiliary requests.

IV. The board issued a communication pursuant to Article 15(1) RPBA, in which objections *inter alia* under Articles 56 and 84 EPC were raised by the board (Article 111(1) EPC).

V. In reply, the appellant submitted a letter dated 30 August 2016, accompanied by a new main request, and renumbered the previous main request as auxiliary request 3. The appellant later informed the board that he would not be represented at the oral proceedings.

VI. Oral proceedings took place on 6 October 2016 in the absence of the appellant. At the end of the proceedings the Chairwoman announced the decision of the board.

VII. The following documents are relevant to the present decision:

D1: EP 1 293 514

D2: WO 99/54440

D3: Kipriyanov S. M. et al., Journal of Molecular Biology, 27 June 2003, 330(1), 99-111.

VIII. Claims 1 to 3 of the main request read:

"1. A pharmaceutical composition comprising a bispecific single chain antibody construct, said bispecific single chain antibody construct comprising binding domains which are capable of specifically binding to human CD3 and human CD19, wherein the corresponding variable heavy chain regions (V_H) and the corresponding variable light chain regions (V_L) regions are arranged, from N-terminus to C-terminus, in the order,

V_H(CD19)-V_L(CD19)-V_H(CD3)-V_L(CD3) or
V_H(CD3)-V_L(CD3)-V_H(CD19)-V_L(CD19)

wherein said bispecific single chain antibody construct comprises an amino acid sequence selected from the group consisting of

(a) an amino acid sequence as depicted in SEQ ID NOs 2 or 10;

(b) an amino acid sequence encoded by a nucleic acid sequence as shown in SEQ ID NOs 1 or 9;

wherein said bispecific single chain antibody construct is obtainable by culturing a CHO cell transformed or transfected with a vector comprising a nucleic acid encoding said bispecific single chain antibody construct that is operatively linked to expression

control sequences allowing expression of said bispecific single chain antibody construct in said CHO cell and recovering the produced bispecific single chain antibody construct from the culture by immobilized metal affinity chromatography and gel filtration, wherein the main product has a molecular weight of ca. 52 kDa under native conditions as determined by gel filtration in PBS.

2. The pharmaceutical composition of claim 1, wherein said variable domains are connected by additional linker sequences.

3. A pharmaceutical composition according to claims 1 or 2, further comprising a proteinaceous compound capable of providing an activation signal for immune effector cells".

IX. The appellant's arguments may be summarised as follows:

Amendments - Article 123(2) EPC

In claim 1 of the new main request, in the final "wherein" clause (i) the host cell was limited to be a CHO cell and (ii) the recovery of the bispecific single chain antibody construct was characterised to result through immobilised metal affinity chromatography and gel filtration in a main product (bispecific single chain antibody construct) having a molecular weight of ca. 52 kDa under native conditions as determined by gelfiltration in PBS, and alternatives (c) and (d) were cancelled. Claims 6, 9 and 10 were editorially amended so as to be in line with the wording of the purpose-related product claim 5.

The subject-matter of the new main request was based on original claims 1, 9 and 17 as well as on page 19, lines 14 to 22, page 32, line 21 and page 33, lines 16 to 18 of the application as filed.

Claim construction

Claim 1 of the main request was for a composition comprising a bispecific single-chain antibody construct having a specific amino acid sequence. This sequence contained

- a 15 amino acid linker between the V_H and V_L region of the CD19 and CD3 binding domain, respectively, and

- a 5 amino acid linker between the CD19 and CD3 binding domain.

The 15 amino acid linker between V_H and V_L regions allowed both domains to properly build functional CD19 and CD3 binding domains.

The 5 amino acid linker between both binding domains (CD19 and CD3) provided for rigidity to prevent the molecule from folding back on itself.

As a consequence of the molecule's structural features and because the claim made reference to a specific purification scheme, the antibody construct as claimed was a monomeric bispecific single-chain antibody molecule, as also reflected by the molecular weight of "*ca. 52 kDa*". Dimeric, tetrameric or higher-meric forms of bispecific single-chain antibody molecules were not encompassed by claim 1.

Inventive step - Article 56 EPC

Closest prior art

In the decision under appeal the examining division had regarded either document D1 or document D3 as representing the closest prior art. This choice was incorrect. Document D1 related to multimeric constructs and was therefore conceptually totally different from the claimed invention. Furthermore, the antibodies disclosed in document D1 had a linker of less than 12 amino acids between at least one V_H/V_L pair. A linker of this length did not allow formation of a functional V_H/V_L pair in a monomeric configuration.

Document D3 disclosed bispecific diabodies and monomeric single-chain antibodies (scFv), both binding to CD3 and CD19. Some of the scFv molecules disclosed had domain arrangements identical to those of claim 1 of the main request. However, these scFv molecules had linkers of 18 or 22 amino acids in length between the V_H and V_L domain, while claim 1 required a linker of 15 amino acids in length. Moreover, the scFv constructs of document D3 had linkers of 27 or 12 amino acids in length between the CD19 and CD3 binding domain, while claim l required linkers of 5 amino acids in length in this position. Finally, document D3 disclosed production of all of its tested constructs in *E. coli*, while the claimed constructs were produced in CHO cells.

In terms of function, the scFv molecules disclosed in document D3 did not bind CD3 (see page 101, right

column, last paragraph), while claim 1 required that the antibody construct binds both CD19 and CD3.

Document D2 on the other hand disclosed antibody constructs that shared all the structural and functional features of the antibody constructs defined in claim 1 except for the variable region arrangement.

Thus, the antibody constructs disclosed in document D2 had the same purpose as the claimed invention and had the fewest structural differences. Document D2 should therefore be taken to represent the closest prior art for assessing inventive step of the claimed invention.

The technical problem

Antibodies having the variable region arrangement set out in claim 1 displayed a better cytotoxic activity (effect) on CD19-expressing NALM 6 cells than construct #1 (see Example 4 and Figure 7 of the application as filed). Construct #1 represented the closest prior art and corresponded to the construct mentioned in document D2 (see Example 2).

On the basis of the structural and functional differences between the antibody construct representing the closest prior art and the subject matter of claim 1, the objective technical problem was the provision of bispecific single-chain CD19xCD3 antibodies with improved cytotoxic activity.

Obviousness

Starting from the bispecific single-chain antibody constructs disclosed in document D2, the skilled person would not have considered it obvious to provide

antibody constructs having the domain arrangement required by claim 1 because they had no motivation to further adjust the already outstanding therapeutic effects of said construct (see document D2, Examples 5 and 7). Moreover, the skilled person would not have known whether altering the domain arrangement would have any an influence on the construct's cytotoxic activity.

Even accepting, for the sake of argument, that the skilled person had attempted to provide an antibody construct with improved cytotoxic activity starting from the construct disclosed in document D2, he would have had to choose between seven options of possible arrangements of the V_H/V_L domains for a potential CD19xCD3/CD3xCD19 bispecific single-chain antibody. In the absence of any teaching in the art, the skilled person would not have known which of those 7 options, if any, would bring about the desired effect. Thus, it would not have been obvious to the skilled person which of the available options for domain arrangements would led to antibody constructs with improved cytotoxic activity vis-à-vis the constructs of the closest prior art.

X. The appellant requested that:

- its main request, filed together with letter of 30 August 2016, be admitted into the proceedings,
- the previous main request become auxiliary request 3,
- the decision under appeal be set aside and a patent be granted on the basis of the set of claims filed as main request together with the letter dated 30 August 2016, or alternatively on the basis of one of auxiliary requests 1 to 3.

Reasons for the Decision

1. The appeal proceedings were continued in the absence of the appellant, in accordance with Rule 115(2) EPC and Article 15(3) RPBA and, accordingly, the appellant was treated as relying on its written case.

Main request

Admission into the proceedings

2. This claim request was filed in response to the board's communication pursuant to Article 15(1) RPBA in which the board raised objections *inter alia* on issues regarding Articles 56 and 84 EPC. The claim request is therefore admitted into the appeal proceedings (Article 13(1) RPBA).

Claim 1

Amendments - Article 123(2) EPC

3. The subject-matter of claim 1 can be derived from the disclosure in claims 1 and 9 in combination with the disclosure on page 19, lines 14 to 22 and page 32 Example 2, of the application as filed. The amendments meet the requirements of Article 123(2) EPC.

Claim construction

4. The claim is for a pharmaceutical composition characterised by the bispecific single-chain antibody construct that it comprises. This in turn is characterised by the presence of binding domains which are capable of specifically binding to human CD3 and

human CD19. The variable regions are structurally defined by the order of the V_H and V_L domains and by the amino acid sequence of the variable regions (SEQ ID NO: 2 or 10) or of the encoding nucleic acid sequence (SEQ ID NO: 1 or 9).

5. Furthermore, the antibody construct is defined as obtainable by culturing in CHO cells and is therefore subject to eukaryotic post-processing, including correct folding and glycosylation. Finally, the antibody has a molecular weight of ca. 52 kDa, limiting the claimed constructs to monomeric structures and excluding multimers.

Clarity and support in the description - Article 84 EPC
Disclosure of the invention - Article 83 EPC

6. The board has no objections with respect to Articles 83 or 84 EPC as regards claim 1. Concerning Article 83 EPC, the board notes that Example 3 and Figures 6b and 6d of the application provide evidence that single chain antibody constructs as claimed are able to specifically bind both CD3 and CD19.

Inventive step - Article 56 EPC

Closest prior art

7. The closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (see Case Law of the Boards of Appeal of the EPO, 8th edition 2016, I.D.3.1).

8. The purpose of the invention of claim 1 is to provide a pharmaceutical composition for the treatment and or amelioration of B-cell related or B-cell mediated disorders (see page 5, paragraph 1 of the application).

9. Document D2 discloses bispecific antibody constructs which are capable of specifically binding to human CD3 and human CD19 which differ from those presently claimed only in the domain arrangement. The constructs disclosed in document D2 have the domain arrangement

V_L(CD19)-V_H(CD19)-V_H(CD3)-V_L(CD3) (see Example 2 of document D2)

as opposed to the antibody constructs defined in present claim 1 which have the domain arrangement of either

V_H(CD19)-V_L(CD19)-V_H(CD3)-V_L(CD3) or
V_H(CD3)-V_L(CD3)-V_H(CD19)-V_L(CD19).

10. The invention disclosed in document D1 relates to multimeric variable fragment (Fv)-antibody constructs and, in particular, to the provision of multimeric antibodies with at least four binding domains which are mono- or multi-specific. A preferred embodiment is a bispecific antibody capable of binding CD19 and CD3 (see document D1, paragraph [0025] and claim 14). The document discloses examples of such antibodies having the domains arranged in the order V_H(CD3)-V_L(CD3)-V_H(CD19)-V_L(CD19) and V_H(CD3)-V_L(CD3)-V_H(CD19)-V_L(CD19) (see Example 1 and Figures 4 and 5). However, these antibody constructs are multimeric (see Example 1, paragraph [0047]). As noted by the appellant, document D1 also discloses monomeric

antibody constructs with the same domain arrangements as the presently claimed antibody constructs, but discloses no detailed structural information or any information on the binding ability, let alone the cytotoxic activity of these constructs.

11. Document D3 discloses a bispecific single-chain antibody with the domain arrangement: V_H(CD3)-V_L(CD3)-V_H(CD19)-V_L(CD19) (see document D3, Figure 1). This is the same arrangement as the claimed antibody constructs. The antibody disclosed in document D3 is not bispecific, binding only CD19 (see page 105, column 1). Structural differences between the construct disclosed in document D3 and those claimed include

- a linker between the V_H and V_L domains (see figure 1 of document D3) of 18 amino acids compared to 15 amino acids in length (present claim 1).

- a linker between the CD19 and CD3 binding domain of 27 amino acids in length (see page 103 of document D3, right column) compared to a linker of 5 amino acids in length (present claim 1).

- differences e.g. in folding and post-translation processing due to expression in bacterial cells (see page 100 of document D3, right column) compared with expression in CHO cells of the presently claimed constructs.

12. Thus, while documents each of D1, D2 and D3 aim to provide bispecific antibody constructs capable of specifically binding to human CD3 and human CD19 and are therefore useful for the treatment and or amelioration of B-cell related or B-cell mediated disorders, the constructs disclosed in document D2 have

more structural features in common with the claimed constructs and may be taken as representing the closest prior art for subject-matter of claim 1.

The technical problem to be solved

13. The claimed antibody constructs differ from those representing the closest prior art in the domain arrangement. The effect of this difference is that the former display a higher cytotoxic activity (effect) on CD19-expressing NALM 6 cells than construct #1 (representing the closest prior art) at certain concentrations of antibody. This is demonstrated in Example 4 and Figure 7 of the application, which shows that construct #6 and construct #2 (embodiments of present claim 1) have respectively about 2 times and about 4 times higher specific lysis at concentrations of about 5 pg/ml and about 1.5 times and about 2 times higher specific lysis at concentrations of about 10 pg/ml, than construct #1.

14. In view of the above differences and the technical effects thereof, the board, in agreement with the appellant (see section VI) considers that the technical problem to be solved by the composition of claim 1 may be formulated as the provision of bispecific single-chain CD19xCD3 antibodies with improved cytotoxic activity.

Obviousness

15. The question to be answered by the board is therefore whether the skilled person, faced with the above formulated technical problem and starting from bispecific antibody constructs disclosed in document D2, would have considered it obvious to provide the

claimed antibody constructs. In other words, it is to be considered whether there was any teaching in the art that would have suggested to the skilled person that rearranging the order of the binding domains to the particular order present in the antibody constructs now claimed, would lead to antibodies with improved cytotoxic activity.

16. Single-chain antibodies having the same domain arrangement as the antibody constructs of claim 1 were disclosed in document D3 (see Figure 1). However, as noted above, these were not bi-functional (see document D3, page 105, left column). The skilled person seeking to improve the bifunctional antibodies disclosed in document D2 is unlikely to have adopted the domain arrangement of mono-functional antibodies disclosed in document D3, since this was not associated with an expectation that it would be useful to improve existing bifunctional antibodies.

17. Document D1 also discloses antibody constructs having the same domain arrangement as the claimed antibody construct (see Figures 4 and 5). However, document D1 does not disclose the binding specificity of these antibodies and they are not monomeric. The skilled person seeking to improve monomeric bifunctional antibodies would not have found any teaching in document D1 that would have suggested that the domain arrangements of the antibody constructs now claimed would have been good candidates for solving the technical problem at hand.

18. In view of the above, the board is satisfied that the the skilled person would not have considered it obvious to provide the antibody constructs of claim 1. The requirements of Article 56 EPC are therefore fulfilled. This conclusion applies equally to dependent claims 2 and 3.

Remittal - Article 111(1) EPC

19. The decision under appeal dealt only with the subject-matter of the claims for a pharmaceutical composition comprising a bispecific single chain antibody construct (products). The decision did not deal with subject-matter for processes for the production or medical use of said compositions. The examination of this subject-matter for compliance with the EPC may require different or additional considerations in comparison with the product of claim 1 and dependent claims 2 and 3. The board therefore exercises its power under Article 111(1) EPC to remit the case to the examining division for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division for further prosecution on the basis of the set of claims of the main request filed together with the letter dated 30 August 2016.

The Registrar: The Chairwoman:

D. Hampe G. Alt

Decision electronically authenticated