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Datasheet for the decision of 10 May 2016

Case Number: T 1059/12 - 3.3.04

Application Number: 05755389.3

Publication Number: 1761565

IPC: C07K16/24

Language of the proceedings: EN

Title of invention:
Compositions and methods for treating inflammatory disorders

Applicant:
Domantis Limited

Headword:
Single domain antibody/DOMANTIS

Relevant legal provisions:
EPC Art. 56, 123(2)

Keyword:
Main request - inventive step (no)
Auxiliary request 1 - amendments allowable (no)
Auxiliary request 2 - inventive step (no)

Decisions cited:

Catchword:

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Case Number: T 1059/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 May 2016

Appellant: (Applicant)	Domantis Limited 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Representative:	Lock, Graham James Fry Heath & Spence LLP The Gables Massetts Road Horley Surrey RH6 7DQ (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 23 November 2011 refusing European patent application No. 05755389.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. The appeal of the applicant ("appellant") lies against the decision of the examining division to refuse European patent application No. 05755389.3, which was filed as an international application and published as WO 2006/003388.

II. The impugned decision was based on a main (sole) request which was held by the examining division to fail the requirements of Articles 54 and 56 EPC.

III. With its statement of grounds of appeal the appellant filed a main request and two auxiliary requests.

Claim 1 of the main request is identical to claim 1 of the main request before the examining division and reads:

"1. A single domain antibody polypeptide construct comprising first and second anti-TNFα single domain antibodies and an anti-serum albumin single domain antibody."

Claim 1 of auxiliary request 1 reads:

"1. A single domain antibody polypeptide construct comprising first and second anti-TNFα single domain antibodies and an anti-serum albumin single domain antibody, wherein the construct binds human TNFα with a Kd of < 100nM."

Claim 1 of auxiliary request 2 reads:

"1. The use of a composition comprising a single domain antibody polypeptide construct comprising first and

second anti-TNFα single domain antibodies and an anti-serum albumin single domain antibody that antagonizes human TNFα's binding to a receptor in vitro for the preparation of a medicament for the treatment, prevention, inhibition of progression or delay in the onset of a TNFα-related inflammatory disorder in an individual suffering from such a disorder."

IV. The appellant was summoned to oral proceedings and subsequently informed of the board's preliminary opinion in a communication according to Article 15(1) RPBA.

V. At the oral proceedings before the board on 10 May 2016 the appellant was absent, as communicated to the board in its letter of 3 February 2016. They were thus held in accordance with Rule 115(2) EPC and Article 15(3) RPBA. At the end of the oral proceedings the chairwoman announced the board's decision.

VI. The following documents are cited in this decision:

D1 WO2004/003019

D4 WO2004/041862

VII. The arguments of the appellant submitted in writing and relevant for the present decision may be summarised as follows:

Main request

Inventive step

There were a number of technical reasons that would have dissuaded a skilled person from modifying a

molecule consisting of two single domain antibodies to include a further one. The following issues complicated the design and production of such a trivalent molecule with separate antigen-binding activities:

- The formation of "Holiday structures" and consequent deletion of sequence fragments from the clone.
- The expression of a genetic fusion construct at sufficient levels.
- The purification of the construct.
- Aggregation issues due to irreversible, concentration driven self-association of the construct.

It was conceivable that addition of a serum albumin (SA) binding domain to two antigen binding domains caused incompatible steric hindrance ultimately resulting in sub-optimal, non-sufficient affinity and efficacy.

Examples 18 to 21 of the application demonstrated the remarkable *in vivo* efficacy of the claimed constructs. Accordingly, the technical effect linked to the claimed constructs comprising two TNFα-binding single domains and one binding to serum albumin was the remarkable *in vivo* efficacy as compared to the gold-standard drugs on the market. Therefore, the objective technical problem was the provision of a construct useful for treating rheumatoid arthritis and having such remarkable *in vivo* efficacy.

Document D4 as closest prior art

While document D4 disclosed that bivalent, monospecific anti-TNFα single domain antibodies, referred to in document D4 as "VHH", had increased avidity and higher antagonistic efficacy than their monovalent

counterparts, it also disclosed that mono-, bi- and trivalent anti-TNFα VHH all had lower antagonistic efficacy than Enbrel®, while only the tetravalent anti-TNFα VHH had higher antagonistic efficacy. Therefore, document D4 taught the skilled person away from selecting the bivalent anti-TNFα single domain antibody as the most promising starting point for designing a rheumatoid arthritis drug with remarkable *in vivo* activity.

Even if the skilled person had started from a bivalent anti-TNFα VHH as disclosed in document D4, it was not correct to assume that he would have logically considered adding a serum albumin single binding domain to these constructs because the binding activity of such a trivalent, bi-specific molecule could not have been predicted with any reasonable expectation of success.

For example, the skilled person was aware of the phenomenon of steric hindrance. Indeed, document D4 had compared the monovalent and bivalent anti-TNFα VHH formats to a fusion protein consisting of an anti-TNFα-VHH and the CH1-deleted Fc portion of an IgG antibody. It was found that the fusion protein was five times less effective than the bivalent VHH, and that steric hindrance by the bulky Fc tail might be the cause (see Example 4 and page 58, lines 3 to 6). Thus, document D4 taught away from incorporating a different additional single domain antibody, such as one binding to serum albumin, into the bivalent anti-TNFα VHH single domain antibodies, and there was no pointer or suggestion in document D4 that such a construct, were it to be made, would have high efficacy *in vivo*.

Document D1 as closest prior art

Document D1 disclosed single domain antibodies, referred to as "dAb", and in particular a construct comprising an anti-TNFα (TAR1-5-19) and an anti-mouse serum albumin single domain antibody, both linked via a disulphide bond (see example 12). It was not correct to assume that a skilled person would have logically considered adding an additional anti-TNFα dAb to this construct. The binding activity of such a trivalent, bi-specific molecule could not have been predicted by a skilled person aware of the phenomenon of steric hindrance.

Auxiliary request 1

The claims of this request were similar to the claims of the main request, but they required the claimed construct to bind human TNFα with a Kd of <100 nM. This feature was supported by the application as filed, at page 14, lines 12 to 22.

Auxiliary request 2

The claims of this request were similar to the claims of the main request, but the independent claims were directed to the uses referred to in the dependent claims of the main request.

VIII. The appellant requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request or, alternatively, of one of auxiliary requests 1 or 2, all filed together with the statement of grounds of appeal on 3 April 2012.

Reasons for the Decision

1. The duly summoned appellant did not attend the oral proceedings, as communicated to the board by its letter of 3 February 2016. The board considered it expedient to hold the scheduled oral proceedings in the appellant's absence in order to reach a final decision in this appeal case. The appellant was then treated as relying on its written case in accordance with Rule 115(2) EPC and Article 15(3) RPBA.

Introduction and terminology

2. The present invention is in the area of single domain antibodies and their therapeutic use. Examples of single domain antibodies include heavy chain variable domains derived from antibodies naturally devoid of light chains, single domain antibodies derived from conventional four-chain antibodies, or engineered antibodies (see document D4, page 4, lines 10 to 13). Serum from animals of the Camelid family contains functional antibodies that are naturally devoid of light chains. The antigen-binding site of these heavy chain antibodies is formed only by a single domain, designated "VHH" (document D4, page 4, line 17). VHHs are easily produced as recombinant proteins. Antigen binding single V_H domains have also been identified from, for example, a library of murine V_H genes amplified from genomic DNA from the spleens of immunised mice and expressed in *E. coli*. The isolated single V_H domains have been termed "dAbs" for "domain antibodies" (see e.g. present application, page 6, second paragraph). Single domain antibodies can be used as modular building blocks for generating multivalent and/or multispecific antibody constructs, whereby "multivalent" means that the construct encompasses more

than one single domain antibody and "multispecific" means that it encompasses single domain antibodies of more than one binding specificity.

3. The cytokine tumour necrosis factor alpha (TNFα) has an important role in the pathogenesis of rheumatoid arthritis (RA), an autoimmune inflammatory disease. At the priority date of the application anti-TNFα biologicals used in the treatment of RA included the chimeric antibody infliximab (marketed as Remicade®), the human monoclonal antibody adalimumab (Humira®), and the TNFR-IgG-Fc fusion protein etanercept (Enbrel®).

Main request

Inventive step (Article 56 EPC)

Closest prior art

4. 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, 7th edition 2013, section I.D.3.1).

5. The present invention pertains to the provision of a single domain antibody polypeptide construct that binds TNFα, has an increased half-life *in vivo* and can be used for the treatment of inflammatory disorders including RA (see page 1 of the description, first paragraph). The examining division considered that either document D1 or document D4 could be considered

to represent the closest prior art.

6. Document D1 discloses the preparation of monospecific bivalent and trivalent dAbs. The preparation of anti-TNFα dAb homodimers is described on page 99, line 1 to page 108, line 14 while example 8 discloses anti-TNFα dAb homotrimers. Example 12 describes a method for making a dual-specific antibody specific for both mouse serum albumin and TNFα by chemical coupling of an anti-mouse serum albumin dAb and an anti-TNFα dAb. Although the treatment of inflammatory diseases, e.g. RA, is mentioned once on page 33, lines 15 to 20, there is no reference to any specific dAb in this context. Thus, while document D1 shares relevant structural features of the invention, it is primarily concerned with the preparation of bivalent dAbs and not with their use for the treatment of inflammatory disorders. It thus has a different purpose from the claimed invention.

7. Document D4 on the other hand discloses polypeptides comprising one or more single domain antibodies directed towards TNFα (anti-TNFα VHH) and also their use in the therapy of inflammatory disorders such as RA (see page 1, 1st and 2nd paragraphs). According to document D4, the antagonistic activity of the anti-TNFα dimeric VHH and trimeric VHH is higher than that of Remicade®, while that of the tetravalent VHH is even better than Enbrel® in a cell-based assay (see example 4). Document D4 further discloses that the *in vivo* half-life of an anti-TNFα VHH is increased by adding a single domain antibody directed against a serum protein to it (page 17, 2nd paragraph). The board concludes that document D4 not only discloses single domain antibodies which share relevant technical features with the claimed invention but also relates to

the same purpose as the claimed invention. Therefore document D4 is the closest prior art.

The technical problem to be solved

8. The claimed construct differs from the constructs disclosed in document D4 in that it additionally comprises an anti-serum albumin single domain antibody. Concerning the technical effect related to this difference, the application discloses that the anti-serum albumin single domain antibody acts to increase the half-life of the polypeptide *in vivo* (see e.g. page 16, second paragraph).

9. The appellant submitted that the objective technical problem was the provision of a construct useful for treating RA and having remarkable *in vivo* efficacy compared to the gold-standard drugs on the market.

10. The board is not persuaded by this line of argument. The effects relied on by the appellant in its formulation of the problem were obtained with specific constructs (see examples 18 to 21 of the application), while claim 1 relates generically to any single domain antibody polypeptide construct comprising first and second anti-TNFα single domain antibodies and an anti-serum albumin single domain antibody, regardless of its *in vivo* efficacy. Indeed, the efficacy of the construct is not a limiting feature of claim 1. Moreover, it is apparent from the application itself that not all constructs encompassed by claim 1 have a remarkable *in vivo* efficacy. Thus the application discloses (see page 244, second paragraph) that of all the anti-TNFα dAb molecules tested only "the most effective anti-TNF dAb formats are either equivalent to or more effective than HUMIRA, and the most effective

anti-TNF dAb formats are significantly more effective than ENBREL in all studies". In other words, as regards the subject-matter of claim 1, the "remarkable *in vivo* efficacy as compared to the marketed gold standard drugs" is merely an alleged advantage which cannot be taken into consideration in determining the problem underlying the invention. As the subject-matter of claim 1 is not restricted to the "most effective anti-TNF dAb format" identified in the application the problem has to be reformulated in a less ambitious way.

11. In the board's judgement, starting from document D4, the technical problem to be solved can be formulated as the provision of a construct comprising two anti-TNFα single domain antibodies and having an increased serum half-life. The board is satisfied that the subject-matter of claim 1 solves this technical problem.

Obviousness

12. The question is whether the skilled person faced with the technical problem defined in point 11 above would have modified the teaching in the closest prior art document so as to arrive at the claimed invention in an obvious manner.

13. Document D4 discloses not only polypeptide constructs comprising two anti-TNFα VHH, and their remarkable avidity, but also (see page 17, lines 4 to 8) that "an anti-TNF polypeptide as described herein further comprising one or more single domain antibodies directed against one or more serum proteins of a subject, surprisingly has significantly prolonged half-life in the circulation of said subject compared with the half-life of the anti-TNF-alpha single domain antibody when not part of said construct." Importantly,

document D4 also discloses (see page 17, lines 10 to 12) that the polypeptides were found to "exhibit the same favorable properties of single domain antibodies such as high stability remaining intact in mice, extreme pH resistance, high temperature stability and high target affinity." Examples of such polypeptide constructs are depicted in Table 5 of document D4 and include single domain antibodies directed against mouse serum albumin in combination with TNFα VHH.

14. Starting from the teaching of document D4 and faced with the problem of providing a construct comprising two anti-TNFα single domain antibodies and having an increased serum half-life, the skilled person aware from document D4 of the effect of single domain antibodies directed against serum albumin would have readily considered including an anti-serum albumin single domain antibody in constructs comprising two anti-TNFα VHH.

15. The appellant submitted that there were a number of technical reasons that would have dissuaded a skilled person from modifying a molecule comprising two single domain antibodies to include a further single domain antibody.

15.1 The board is not persuaded that any of the reasons put forward by the appellant (see section VII above) would have deterred the skilled person from including an anti-serum albumin single domain antibody in constructs comprising two anti-TNFα VHH. As a matter of fact, both document D1 (see example 8) and document D4 (see example 4) provide trimers and tetramers of single domain antibodies without reporting any of the hypothetical problems envisaged by the appellant. Thus, document D4 e.g. reports (see page 56, lines 10 to 30)

the construction of production vectors for bivalent, trivalent and tetravalent derivatives. After transformation in *E. coli* the resulting clones were screened by PCR and it was confirmed that only correctly orientated inserts were obtained. The clones were grown on a 50 ml scale, periplasmic fractions prepared and the products purified. Document D4 reports that good production levels of intact multivalent VHH were achieved (page 56, lines 26 to 28).

15.2 Document D4 moreover discloses that whereas multivalent constructs are difficult to produce with conventional antibodies, and that, due to bulky subunits, functionality will be lost or greatly diminished, more than two single domain antibodies can be linked to each other and functionality is even increased considerably compared to the monovalent construct (see page 21, last paragraph and example 4). Finally, steric hindrance was found only with VHH-Fc fusions, not with bivalent VHHs, suggesting that the bulky Fc tail led to steric hindrance (see document D4, example 4). Therefore document D4 provides not only a clear incentive for the skilled person to include an anti-serum albumin domain antibody in constructs comprising two anti-TNFα VHH in order to increase their serum half-life, but also a reasonable expectation of success.

16. In summary, the board concludes from the above that the skilled person would have arrived in an obvious manner at the subject-matter of claim 1. Therefore, the main request fails to meet the requirements of Article 56 EPC.

Auxiliary request 1

Article 123(2) EPC

17. Claim 1 has been amended to include the feature "wherein the construct binds human TNFα with a Kd of < 100nM". The appellant indicated page 14, lines 12 to 22 of the application as filed as providing a basis for the feature.

17.1 The passage in question discloses that "in another embodiment, the single domain antibody polypeptide construct comprises a human single domain antibody polypeptide. In another embodiment, the human single domain antibody polypeptide binds TNFα. In another embodiment, the single domain antibody polypeptide construct binds human TNFα with a Kd of <100 nM. In another embodiment, the single domain antibody polypeptide construct binds human TNFα with a Kd in the range of 100 nM to 50 pM. In another embodiment, the single domain antibody polypeptide construct binds human TNFα with a K_d of 30 nM to 50 pM. In another embodiment, the single domain antibody polypeptide construct binds human TNFα with a K_d of 10 nM to 50 pM. In another embodiment, the single domain antibody polypeptide construct binds human TNFα with a K_d in the range of 1 nM to 50 pM."

17.2 The feature in question has thus been disclosed in combination with a single domain antibody polypeptide construct which comprises a human single domain antibody polypeptide that binds TNFα, but not in combination with the construct of claim 1, i.e. a single domain antibody polypeptide construct comprising first and second anti-TNFα single domain antibodies and an anti-serum albumin single domain antibody. Therefore

this passage cannot provide a basis for the claimed combination of features.

18. The board concludes that the subject-matter of claim 1 fails to meet the requirements of Article 123(2) EPC.

Auxiliary request 2

Article 56 EPC

19. Claim 1 of this request is directed to the use of a composition comprising a single domain antibody polypeptide construct comprising first and second anti-TNFα single domain antibodies and an anti-serum albumin single domain antibody that antagonises human TNFα's binding to a receptor *in vitro* for the preparation of a medicament for *inter alia* the treatment of a TNFα-related inflammatory disorder.

20. Document D4 is considered to represent the closest prior art. It relates to polypeptides comprising one or more single domain antibodies directed towards TNFα and their use in the therapy of inflammatory disorders such as RA (see also point 7 above). In example 4 the antagonistic efficacy of bi-, tri- and tetravalent VHH against human and mouse TNF-alpha was tested. It was found that increasing the avidity of the VHH from monomer to dimer, trimer and tetravalent format led to an improvement in the antagonistic properties of the molecule.

21. The subject-matter of claim 1 thus differs from document D4 in that the construct employed in the composition according to claim 1 additionally comprises an anti-serum albumin single domain antibody. Concerning the technical effect related to this

difference, the application discloses that the anti-serum albumin single domain antibody acts to increase the half-life of the polypeptide *in vivo* (see e.g. page 16, second paragraph).

22. Starting from document D4, the technical problem to be solved can be formulated as the provision of means which antagonise human TNFα's binding to a receptor *in vitro* and which have an increased serum half-life *in vivo*. The board is satisfied that the subject-matter of claim 1 solves the technical problem.

23. As set out above (see points 13 to 15.2), document D4 provides not only polypeptide constructs comprising two anti-TNFα single domain antibodies which have a high antagonistic activity but also an incentive to include an anti-serum albumin single domain antibody in anti-TNFα VHH in order to increase their serum half-life *in vivo* and a reasonable expectation that this approach will succeed. The skilled person faced with the problem formulated above and aware of the teaching of document D4 would thus have arrived in an obvious manner at the claimed subject-matter.

24. The appellant failed to provide any arguments (see section VII above) which might have persuaded the board otherwise.

25. In summary, the board concludes from the above that claim 1 of auxiliary request 2 fails to meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated