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Datasheet for the decision of 21 January 2015

Case Number: T 1264/10 - 3.3.04

Application Number: 03738294.2

Publication Number: 1517921

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Language of the proceedings: EN

Title of invention:
Dual specific ligands with increased serum half-life

Patent Proprietor:
Domantis Limited

Opponents:
Affibody AB
Ablynx N.V.

Headword:
Dual specific ligands/DOMANTIS

Relevant legal provisions:
EPC Art. 56

Keyword:
"All requests - inventive step (no)"

Decisions cited:

Catchword:

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Case Number: T 1264/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 21 January 2015

Appellant: (Patent Proprietor)	Domantis Limited 980 Great West Road Brentford Middlesex TW8 9GS (GB)
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Representative:	Taormino, Joseph Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 8 April 2010 revoking European patent No. 1517921 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	B. Claes
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The appeal was lodged by the patent proprietor (hereinafter "appellant") against the decision of the opposition division to revoke European patent No. 1 517 921. The patent with the title "*Dual specific ligands with increased serum half-life*" was granted for the European patent application 03738294.2, published as WO 2004/003019.

II. Two oppositions were filed requesting the revocation of the patent on the grounds for opposition pursuant to Article 100(a) EPC, in conjunction with Articles 54 and 56 EPC, and Articles 100(b) and (c) EPC.

III. The opposition division decided *inter alia* and with respect to an amended auxiliary request 2, filed during the oral proceedings before the opposition division, that the subject-matter of claims 1 and 2 did not involve an inventive step (Article 56 EPC).

IV. With the statement of grounds of appeal the appellant filed a main request, three auxiliary requests and a number of documents. Claim 1 of the main request was identical to claim 1 of the amended auxiliary request 2 as considered by the opposition division, but for the deletion of the wording "EPO receptor". The appellant argued that the subject-matter of this claim involved an inventive step (Article 56 EPC).

Claim 1 of the main request read:

"1. A dual-specific ligand comprising a first immunoglobulin single variable domain having binding specificity for serum albumin (SA), and a second immunoglobulin single variable domain having binding

specificity for an antigen selected from the group consisting of ApoE, Apo-SAA, BDNF, Cardiotrophin-1, EGF, EGF receptor, ENA-78, Eotaxin, Eotaxin-2, Exodus-2, EpoR, FGF-acidic, FGF-basic, fibroblast growth factor-10, FLT3 ligand, Fractalkine (CX3C), GDNF, G-CSF, GM-CSF, GF-ß1, insulin, IFN-γ, IGF-I, IGF-II, IL-1α, IL-1ß, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8 (72 a.a.), IL-8 (77 a.a.), IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18 (IGIF), Inhibin α, Inhibin ß, IP-10, keratinocyte growth factor-2 (KGF-2), KGF, Leptin, LIF, Lymphotactin, Mullerian inhibitory substance, monocyte colony inhibitory factor, monocyte attractant protein, M-CSF, MDC (67 a.a.), MDC (69 a.a.), MCP-1 (MCAF), MCP-2, MCP-3, MCP-4, MDC (67 a.a.), MDC (69 a.a.), MIG, MIP-1α, MIP-1ß, MIP-3α, MIP-3ß, MIP-4, myeloid progenitor inhibitor factor-1 (MPIF-1), NAP-2, Neurturin, Nerve growth factor, ß-NGF, NT-3, NT-4, Oncostatin M, PDGF-AA, PDGF-AB, PDGF-BB, PF-4, RANTES, SDF1α, SDF1ß, SCF, SCGF, stem cell factor (SCF), TARC, TGF-α, TGF-ß, TGF-ß2, TGF-ß3, tumour necrosis factor (TNF), TNF-α, TNF-ß, TNF receptor I, TNF receptor II, TNIL-1, TPO, VEGF, VEGF receptor 1, VEGF receptor 2, VEGF receptor 3, GCP-2, GRO/MGSA, GRO-ß, GRO-γ, HCC1, 1-309, HER 1, HER 2, HER 3 and HER 4, wherein each of the first and second domains is

(i) a heavy chain variable domain or

(ii) a light chain variable domain."

V. With submissions dated 5 August 2010, 18 November 2010 and 25 February 2011, opponent 02 (hereinafter respondent II) replied to the statement of grounds of appeal and submitted a number of further documents.

VI. With a letter dated 23 July 2012 the appellant maintained the main request as filed with the statement

of grounds of appeal and filed six auxiliary requests replacing the auxiliary requests submitted with the statement of grounds of appeal.

VII. With a letter dated 11 December 2012 respondent II filed further arguments and documents.

VIII. The board summoned the parties to oral proceedings. Subsequently, the appellant filed further letters dated 25 August and 15 December 2014, respondent II further letters dated 8 September, 28 October and 19 and 23 December 2014; and opponent 01 (hereinafter respondent I) submissions dated 17 September 2014 and 8 January 2015. The board issued two communications to the parties, dated 23 December 2014 and 9 January 2015, dealing with procedural issues.

IX. Oral proceedings took place on 20 and 21 January 2015. During the oral proceedings, the appellant filed two new auxiliary requests (auxiliary request I and II) and withdrew all previously filed auxiliary requests. Claim 1 of both new auxiliary requests was identical to claim 1 of the main request (see section IV, above). During the oral proceedings the board heard the parties on the requirements of Articles 54 and 123(2) EPC and Rule 80 EPC in relation to claims 1 to 3 of the main request and auxiliary request I and claim 1 of auxiliary request II and the board expressed its opinion on each of these requirements in relation to these claims. The parties were furthermore heard on the requirements of Article 56 EPC in relation to the subject-matter of (identical) claim 1 of all the appellant's requests. At the end of the oral proceedings the chairwoman announced the decision of the board.

X. The documents cited in this decision are the following:

D1: Conrath *et al*. (2001), J. Biol. Chem., Vol. 276, No. 10, pages 7346-7350.

D2: Smith *et al*. (2001), Bioconjugate Chem., Vol. 12, pages 750-756.

D3: Holliger *et al.* (1997), Nature Biotechnology, Vol. 15, pages 632-636.

D4: WO91/01743

D12: EP-A-0 368 684

D13: Muyldermans (2001), Reviews in Molecular Biotechnology, Vol. 74, pages 277-302.

D48: Dennis *et al.* (2002), J. Biol. Chem., Vol. 277, No. 38, pages 35035-35043.

D53: Half-Life comparison chart submitted by the appellant with letter dated 30 July 2010.

XI. The arguments of the appellant regarding inventive step of the subject-matter of claim 1 of all the requests can be summarised as follows:

Closest prior art

The bispecific and bivalent camel single domain antibody constructs (VHH constructs) as disclosed in document (D1) represented the closest prior art. These constructs were based on small immunoglobulin single variable domains and were structurally very close to the claimed dual-specific ligands. Furthermore, the

disclosure in document (D1) and the claimed invention shared the objective of increasing the therapeutic availability of the construct by increasing its *in vivo* serum half-life.

Document (D2) equally addressed the objective of extending the serum half-life of the respective constructs. The ligands disclosed in document (D2) were however Fab' and $F(ab')_2$ constructs and were thus substantially larger than and conceptually different from the dual-specific small domain antibodies of claim 1. Accordingly, document (D2) could only be selected as to represent the closest prior art with hindsight when knowing the claimed invention.

The problem to be solved

If document (D2) represented the closest prior art, then the problem to be solved was the provision of a conceptually different antibody construct, taking up the principle taught in document (D2) to provide for an *in vivo* half-life improving effect.

Obviousness

The relevant question for obviousness was whether or not the person skilled in the art would apply the concept of serum albumin (SA) binding by antibody constructs in the blood, as disclosed in document (D2), to ligands such as the single domain antibody constructs, e.g. disclosed in document (D1).

The skilled person was taught by document (D1) that the *in vivo* half-life of the disclosed camel domain antibodies, *i.e.* VHH monomers and dimers, was less than two hours (see page 7349, right hand column, lines 15

to 18). This was extremely low in comparison to the *in vivo* half-life of e.g. Fabs which was ca. 31 hours (see document (D2), Table 2) and rendered it questionable whether such extremely short serum *in vivo* half-life would in fact be sufficient to enable such a small domain antibody to bind and be stabilised by serum albumin present in the blood in time before being excluded from the serum.

Both prior art documents (D12) and (D13) addressed improving the *in vivo* serum half-life of single domain antibodies, called ligands in this context. Document (D12) proposed in column 5, lines 5 to 32, in this respect, to mutate or alter the domain antibody itself, e.g. to improve the solubility, or, in column 7, lines 3 to 6, to use strings of domains, effectively increasing the size of the ligand. Document (D13), on page 295, left-hand column, lines 22 to 24, similarly suggested to optimise the pharmacokinetic properties of domain antibodies (here VHH, also referred to e.g. in document (D1)) by engineering their size or oligomeric state. Accordingly, the art was silent about using the ability to bind to SA to improve the serum half-life of small domain antibodies, but rather suggested other solutions than the claimed subject-matter.

Document (D2) itself did not mention applying the therein disclosed principle of extending the half-life of antibody fragment constructs to single domain antibody ligands, although such ligands were known to the skilled person at the relevant date of the patent in suit. It therefore constituted hindsight to apply the principle of document (D2) to single domain antibodies and to arrive at the constructs of claim 1. Indeed, Table 2 in document (D2) taught the skilled person that the improvement in *in vivo* half-life of the

anti-SA-anti-TNF bispecific F(ab')$_2$ as compared to anti-TNF Fab'-cys was only 1.4 times. Such a minimal increase would be recognised by the skilled person as not substantially contributing to a useful increase of the half-life of domain antibodies. In this respect, even an 8 fold increase in the half-life, as was argued by the respondents to be derivable from Table 2 in document (D2), would not be conceived by the skilled person as advantageous given the short half-life as thought in document (D1).

The claimed invention offered surprising advantages as could be taken from document (D53) summarising the half-life increasing effects of the technologies disclosed in documents (D1) to (D4) and document (D48). The claimed invention resulted in *in vivo* serum half-life increases in respect of domain antibodies of 60 to 100 times, compared to the 1.4 increase reported on in document (D2).

XII. The arguments of the respondents regarding inventive step of the subject-matter of claim 1 of all the requests can be summarised as follows:

Closest prior art

Document (D2), identified by the opposition division as the closest prior art, indeed represented the closest prior art for the claimed invention. It addressed the same objective of increasing the serum half-life of immunoglobulin ligands and disclosed the constructs with the highest number of structural features in common with the claimed subject-matter. Indeed the disclosed bispecific F(ab')$_2$ construct specific for SA and TNF constituted the closest construct for assessing inventive step.

The problem to be solved

In view of the fact that there was no technical effect attributable to the difference in conceptual nature of the dual-specific $F(ab')_2$ constructs disclosed in document (D2) and the claimed dual-specific ligands, the problem to be solved was the provision of alternative antibody fragments to those disclosed in document (D2).

Obviousness

The skilled person would be led to replace the immunoglobulin Fab' fragments disclosed in document (D2) by single variable domain immunoglobulins. Both documents (D12) and (D13), which reflected the common general knowledge of the skilled person in this respect, disclosed such alternative immunoglobulin fragment constructs as referred to in claim 1.

The subject-matter of claim 1, a dual-specific ligand, was defined as "comprising" immunoglobulin single variable domains and was not limited to any particular size of the dual-specific ligands. It was thus clear that ligands larger than the small domain antibodies were also within the realm of claim 1.

The data presented in Table 2 and Figures 3 and 5 of document (D2) conveyed the general teaching that it was the specificity for and binding of the disclosed constructs to SA which resulted in the increase of longevity and that this was independent of the size of the construct itself.

The proper reference for determining the increase of *in vivo* serum half-life of the SA-specific $F(ab')_2$ construct disclosed in document (D2) was not the Fab'-cys construct but rather the TNF-specific $F(ab')_2$ construct. Accordingly the relevant increase was much higher than 1.4 times as alleged by the appellant.

XIII. At the end of the oral proceedings the requests of the parties were as follows:

The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request as filed with the statement of grounds of appeal or on the basis of one of auxiliary requests I or II as filed during the oral proceedings.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. During the oral proceedings the board heard the parties on the requirements of Articles 54 and 123(2) EPC and Rule 80 EPC in relation to claims 1 to 3 of the main request and auxiliary request I and claim 1 of auxiliary request II and the board expressed ist opinions for each of these requirements in relation to these claims. However, in view of the board's decision on inventive step (Article 56 EPC) in respect of the subject-matter of claim 1 which is identical and present in all requests (see section IX above and point 4 and further), the board sees no necessity to provide detailed written reasons for these opinions.

3. While the respondents did not object to the admissibility of auxiliary request II filed during the oral proceedings, respondent II challenged the admissibility of auxiliary request I filed earlier during the oral proceedings. The board, however, considered auxiliary request I admissible as the amendments made in claim 2 of that request - which was the deletion of one alternative from the claimed subject-matter - constituted a *bona fide* attempt by the appellant to remedy an issue under Article 123(2) EPC, raised for the first time during the appeal proceedings, relating to the corresponding claim 2 of the main request.

Claim 1 of all requests - inventive step (Article 56 EPC)

4. The opposition division decided that the subject-matter of claim 1 of the then pending amended auxiliary request 2 lacked inventive step (see section III and the impugned decision under appeal on pages 14 and 15).

4.1 It considered that document (D2) represented the closest prior art and that its disclosure differed from the claimed dual-specific ligands by the "*nature of the binding members used*". The technical problem to be solved was accordingly *"the provision of an alternative bispecific binding construct, having one binding member with a specificity for serum albumin and a binding member of the same type with a specificity for TNF-alpha"* (emphasis added by the board).

4.2 Document (D2) conveyed the general teaching that a bispecific ligand, having one binding member which specifically binds to serum albumin (SA), had approximately the same half-life as SA itself due to its binding to SA. The binding of the bispecific agent

to SA resulted in an apparent molecular weight (MW) being at least equal to the MW of SA, *i.e.* which was greater than the normal renal filtration cut-off. The skilled person would thus not fear that using a small single domain antibody, instead of a larger construct, would result in enhanced renal filtration and thus in a reduced half-life of the bispecific ligand. Therefore, small single domain antibodies were known alternatives, among other known binding units, for replacing the Fabs disclosed in document (D2) and the skilled person would have a reasonable expectation that, as an alternative to the Fabs in document (D2), small single variable domains could be used in the bispecific construct.

4.3 As the production of single variable domains was well established in the art (see documents (D12) or (D13)), the subject-matter of claim 1 did not involve an inventive step.

5. The sole amendment in claim 1 as compared to claim 1 of the amended auxiliary request 2 before the opposition division is that, in the present claim, the wording "EPO receptor" is deleted from the group of antigens for which the second immunoglobulin single variable domain can have binding specificity (see section IV). It has not been contested by the parties that the argumentation of the opposition division would equally apply to the subject-matter of claim 1 as now before the board. Indeed, in the board's view the minimal amendment in claim 1 over claim 1 of the amended auxiliary request 2 has no bearing on the pertinence of the examining division's reasoning on the subject-matter now under consideration.

The claimed invention

6. Claim 1 of all the requests before the board is identical. The subject-matter of claim 1 is a dual-specific ligand comprising two immunoglobulin single variable domains, the first one having binding specificity for serum albumin (SA) and the second one having binding specificity for an antigen selected from a particular group, including *inter alia* tumour necrosis factor (TNF), wherein each of the first and second domains is (i) a heavy chain variable domain or (ii) a light chain variable domain (see section IV above).

Closest prior art

7. The first step for assessing inventive step by means of the so-called "problem-solution" approach is to identify the disclosure in the art representing the closest prior art. The parties were not in agreement which cited prior art document represented the closest prior art for the purpose of the assessment of whether or not the subject-matter of claim 1 involved an inventive step. The appellant held that the constructs disclosed in document (D1) represented the closest prior art, whereas the respondents and the opposition division, considered constructs in document (D2) to represent the closest prior art.

8. According to established case law the closest prior art for assessing inventive step by means of the "problem-solution" approach is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as, and having the most structural features in common with, the

claimed invention, *i.e.* requiring the least structural modifications.

9. The objective derivable from the patent in suit as a whole is to provide dual-specific immunoglobulin ligands which comprise immunoglobulin single variable domains, which each have a different specificity (see patent in suit paragraph [0011]). In one part of the description, the patent in suit describes a first configuration which constitutes an improvement of dual-specific ligands, in which one specificity of the ligand is directed towards a protein or polypeptide present *in vivo* in an organism which can act to increase the half-life of the ligand by binding to it (see paragraph [0012]). The board considers that it is this objective which is also addressed by the subject-matter of claim 1 (see point 7 above) in which one specificity of the ligand is directed towards SA, being the exemplified protein which, *in vivo*, can act to increase the half-life of the ligand by binding to it (see paragraph [0363] and annex 1 of the patent in suit).

10. Document (D2) is concerned with "*Prolonged in vivo residence times of antibody fragments associated with albumin*" (see title). The document reports that binding of bacterially derived Fab' antibody fragments to the long-lived protein serum albumin allows full retention of the antibody's binding characteristics while imparting to it serum albumin's longevity *in vivo*. Furthermore, a bispecific $F(ab')_2$ with specificity for rat SA and tumour necrosis factor (TNF) caused a 6-fold increase in AUC (AUC = area under the curve; a measure for the residence time of a protein in the serum *in vivo*) over that of the control in the same experiment, unispecific anti-TNF $F(ab')_2$ without specificity to

albumin (page 754, right-hand column, lines 3 to 7, Figure 5 and Table 2).

11. Document (D1) deals with "*Camel single domain antibodies as modular building units in bispecific and bivalent antibody constructs*" (see title). The document reports on the construction of several bispecific and bivalent antibodies by genetically linking two distinct VHHs - the single binding domains of camel heavy-chain antibodies - with the natural hinge of llama heavy chain antibodies and their performance (see page 7346, right-hand column, penultimate 4 lines). The aim of the study in document (D1) is to address the need for functional bispecific antibody constructs which have a minimal size, lack linker peptides prone to aggregation or susceptible to proteolysis, have high expression yields, high solubility and stability (see page 7346, right-hand column, lines 28 to 31). The document concludes that "[t]*he easy generation steps and the biophysical properties of these bispecific and bivalent constructs based on camel single domain antibody fragments makes them particularly attractive for use in therapeutic or diagnostic programs*" (abstract, penultimate sentence).

12. Having regard to the criteria for determining the closest prior art for a given claimed invention (see point 8 above), the board considers that, seeing that the objective of the claimed invention is an enhanced serum half-life of dual-specific immunoglobulin ligands (see point 9 above) and both specificities of the ligands in document (D2) and claim 1 are identical (*i.e.* specificity towards SA and TNF, see point 10 above), the F(ab') construct as disclosed in document (D2) represents the closest prior art. Indeed, in contrast, document (D1) discloses dual-specific ligands

with different specificities than the claimed subject-matter and does not intentionally aim at providing ligands with an improved half-life.

13. The appellant argued that document (D1) was directed to the assessment of bivalent and bispecific ligands wherein the binding moieties were provided by immunoglobulin single variable domains which were structurally much closer to the claimed dual-specific ligands than the conceptually different and larger Fab' and $F(ab')_2$ constructs as disclosed in document (D2). Furthermore, both documents addressed the objective of extending the serum half-live of the respective constructs, at least in terms of increasing their therapeutic availability. Accordingly, document (D1) represented the closest prior art.

14. In a first aspect, the board notes that claim 1 requires the dual-specific ligand merely to comprise a first and a second immunoglobulin single variable domain (see point 6, above). The claim's wording does not restrict the size of the ligand. In fact, as can be taken from the wording of paragraph [0049] of the patent in suit, the ligands of the invention are not excluded to "*mimic natural antibodies, such as IgG or IgM, or fragments thereof, such as Fv, scFv, Fab or* $F(ab')_2$ *molecules*". The appellant's argument on structural similarity because of the size and the nature of the ligands therefore fails.

15. In a second aspect, the board notes that, in arguing that document (D1) concerns the objective of enhancing the *in vivo* serum half-life of the disclosed bispecific antibody constructs, or at least of increasing their therapeutic availability, the appellant has referred to a number of passages in document (D1), namely: (i) the

last sentence of the abstract which states: "*The easy generation steps and the biophysical properties of these bispecific and bivalent constructs based on camel single-domain antibody fragments makes them particularly attractive for use in therapeutic or diagnostic programs*"; (ii) to the passage on page 7439, right-hand column, under the heading "*Stability in Mouse Plasma*", lines 15 to 18, which states: "*Longer incubation times were not tried, because VHH monomers and dimers have an in vivo half-life of less than 2 hours. Despite this fast clearance, they managed to target specifically the tumor tissue.*"; and (iii) to the passage on page 7350, left-hand column, lines 51 to 58 which states: "*We therefore expect that the high quantities required for tumor therapy and diagnosis will be obtained easily. Extremely high expression levels might be attained more successfully in yeast expression systems, since 300 mg of VHH/liter are routinely produced in fermentors. The recombinant, bispecific, and bivalent constructs obtained by linking two camel single-domain fragments are functional in all respects.*" The board considers that the skilled person, when contemplating the disclosure of document (D1) and in particular the passages referred to by the appellant, would understand that the disclosed bispecific and bivalent constructs provide certain advantages related to their production allowing provision of high quantities required for use in tumor therapy and diagnosis. The board can, however, not concur with the appellant that the disclosure of document (D1) addresses the provision of compounds having an enhanced *in vivo* serum half-life. Accordingly, this argumentation of the appellant considering document (D1), rather than document (D2), as representing the closest prior art also fails.

The problem to be solved and its solution

16. The dual-specific ligand as defined in claim 1 and the the dual-specific $F(ab')_2$ construct as disclosed in document (D2) have the same specificities. The difference between the invention as defined in claim 1 and the dual-specific $F(ab')_2$ ligand of document (D2) lies in the structural nature of the ligand. It was uncontested by the parties that both the prior art ligand and the claimed ligand have a increased *in vivo* serum half-life as compared to the respective similar construct having no specificity for SA.

17. The board can therefore concur with the appellant's arguments presented during the oral proceedings, that the problem to be solved is the provision of a (conceptually) different, and therefore alternative, antibody or immunoglobulin ligand to the SA/TNF bispecific $F(ab')_2$ ligand of document (D2) retaining the prolonged *in vivo* half-life effect described in document (D2).

18. The board is satisfied that the claimed subject-matter solves this problem, in particular in view of the data presented in example 10 of the patent in suit.

Obviousness

19. The decisive question to be answered for the assessment of obviousness in the present case is whether or not the cited prior art contains information or pointers that would guide the skilled person, embarking on solving the problem defined in point 17 above, to modify the dual-specific $F(ab')_2$ ligand of document (D2) in such a way as to arrive at the claimed compounds.

20. Document (D2) concludes in the final sentence on page 755, that: "[i]*n summary, we have shown that association of fragments or derivatives of immunoglobulin with albumin provides the basis of a system for production of a potentially low cost but long-lived therapeutic immunoglobulin".* The board considers this sentence to reflect the general teaching of document (D2), that it is the association with SA as such, irrespective of the size and structure of the construct, which suffices to provide the prolonged half-life feature to the constructs, e.g. of the disclosed the dual-specific $F(ab')_2$ ligand.

21. Part of the humoral immune response of camels and llamas is based largely on heavy-chain antibodies where the light chain is totally absent. These unique antibody isotypes interact with the antigen by virtue of one single heavy chain variable domain, referred to as "VHH". A number of cited documents concern such camel single-domain antibodies, such as documents (D13) and (D1). Document (D13), contains a review of the art of such single-domain camel antibodies at the time just before the relevant date of the patent in suit. It emphasises the use of VHH fragments as modular building blocks for manifold constructs (see the whole of point 2.7.3., starting on page 296). In particular, on page 297, left hand column, lines 41 to 43 the authors "*realise that camelid VHH offer a clear opportunity in each application where bispecific or multivalent antibodies are needed*" and they continue in the sentence bridging the columns on page 297 that: "*VHH are soluble and remarkably robust, allowing a high versatility as building blocks for manyfold constructs.*". Also document (D1) (see also point 11) discloses camel single domain antibodies as modular building units in bispecific and bivalent antibody

constructs (see title). Several bispecific and bivalent antibodies were constructed by geneticall linking two distinct VHHs with the natural hinge of llama heavy-chain antibodies and report on their performance (see page 7346, right-hand column, last sentence).

22. It has not been contested by the parties that claim 1 reads on bispecific and bivalent VHH/VHH constructs, *i.e.* ligands composed of two cameloid heavy-chain variable domains, whereby each VHH has its particular specificity. The board has no reason to be of another opinion.

23. The board considers that the teaching of documents (D1) and/or (D13) would not have escaped the attention of the skilled person faced with the problem as defined for the claimed invention (point 17). The board is, furthermore, satisfied that the skilled person, at the relevant date of the patent in suit, was in a position to produce such ligands as described in document (D13) with specificity for SA and TNF. Neither the former nor the latter have been contested by the appellant either.

24. In the board's judgement, the skilled person, aware of the recognised potential of such constructs (see point 21), would readily consider, when embarking on solving the technical problem as formulated, to replace the dual-specific $F(ab')_2$ ligand disclosed in document (D2) by a bispecific construct on the basis of VHH domains as disclosed in e.g. in document (D13). Furthermore, in the light of the general teaching of document (D2) concerning the SA specificity and its relation to an increased half-life, would have no reservations that also for these constructs the *in vivo* longevity will be enhanced by binding to SA. The skilled person would thus have arrived at dual-specific ligands referred to

in point 22, above, *i.e.* wherein each of the domains is a heavy chain variable domain, in an obvious manner.

25. The appellant has argued that the skilled person would not apply the concept of SA binding in order to provide sufficient serum half-life to ligands which were composed of single-domain antibodies such as e.g. disclosed in documents (D1) and (D13), *i.e.* camel domain antibodies (VHH monomers and dimers).

26. A first line of arguments of the appellant was related to particular technical difficulties which the skilled person would expect to encounter and which would adversely affect the expectation of success.

In a first aspect the appellant submitted that it was known to the skilled person that the *in vivo* serum half-life of VHH monomer and dimer single-domain antibodies was less than two hours (see document (D1), page 7349, right hand column, lines 15 to 18). This was extremely low when compared to the *in vivo* half-life of e.g. Fab' which was ca. 31 hours (see document (D2), Table 2). Table 2 of document (D2) taught the skilled person furthermore that the improvement of the *in vivo* serum half-life of the anti-SA-anti-TNF bispecific $F(ab')_2$ as compared to anti-TNF Fab'-cys was only 1.4 times. Such a minimal increase would be recognised by the skilled person as not to substantially contribute to a useful increase of the half-life of domain antibodies given their short half-life. In fact, even an increase in the magnitude of e.g. eight times, as was allegedly derivable from Table 2 of document (D2), would not be conceived by the skilled person as advantageous.

The appellant argued, in a second aspect, that it was

questionable to a skilled person whether the extremely short *in vivo* serum half-life of domain antibodies, *i.e.* less than two hours, would in fact suffice to enable such a domain antibody to bind to SA and be stabilised in time before being excluded from the serum.

27. The board refers in respect of the first aspect of the line of argument, to what it considers to constitute the general teaching of document (D2) (see point 20), namely that providing binding specificity to SA will, irrespective of the size of the construct, suffice to provide a prolonged *in vivo* serum half-life to the constructs. The board furthermore notes that claim 1 makes no reference to the effectively achieved dimension of the increase of the *in vivo* serum half life, let alone to a reference point for such increase. Accordingly, the board judges that, in the light of the teaching in document (D2), the skilled person would have no hesitation and would expect that constructs falling within the claims and referred to in point 23, would successfully solve the problem as formulated, at least to a certain degree.

28. Concerning the second aspect of the first line of argument of the appellant, the board agrees with the appellant that the passage referred to on page 7349 of document (D1) indeed states that "*... VHH monomers and dimers have an in vivo half-life of less than two hours".* The board notes however, that the next sentence makes clear that "[d]*espite this fast clearance they managed to target specifically the tumour* tissue." The skilled person is thus subsequently taught that binding partners can be successfully targeted by the compounds before clearance from the serum. Accordingly, the board considers that, if the skilled person had had the

concern referred to by the appellant, the skilled person would find comfort in the subsequent disclosure of document (D1) that SA targeting was possible for such constructs.

29. In a second line of argument, the appellant argued that document (D2), which represented the closest prior art, did not consider or suggest applying the disclosed principle of extending the half-life of antibody fragment constructs to single domain antibody ligands, although such ligands were known to the skilled person at the time of the publication of that document. It therefore constituted hindsight to apply the principle of document (D2) to domain antibodies in order to arrive at the constructs to which claim 1 related to.

30. By the same token and in a third line of argument, the appellant argued that the prior art documents (D12) and (D13) addressed the issue of improving the half-life of single-domain ligands. Document (D12) proposed (see column 5, lines 5 to 32) to mutate or alter the domain antibody itself, in order to improve e.g. its solubility, or (see column 7, lines 3 to 6) to use strings of ligands thereby effectively increasing the size of the ligand. Document (D13), on page 295, left-hand column, lines 22 to 24, similarly suggested to optimise the pharmacokinetic properties of domain antibodies (in that case VHH, such as also referred to e.g. in document (D1)) by engineering their size or oligomeric state. The appellant noted that accordingly the art was silent on applying the *in vivo* serum half-life improving concept of document (D2), but rather suggested other solutions than the claimed subject-matter.

31. The board notes in the context of these lines of argument in general that the absence in a given document, which is considered to represent the closest prior art, of a direct pointer to the claimed solution of a technical problem formulated on the basis of this closest prior art would, as such, not constitute a indication that the claimed subject-matter was not obvious to a skilled person and would therefore justify accepting that an inventive step was involved. Indeed such absence would rather necessitate assessing combinations of the teaching of the closest prior art and a further disclosed teaching or the common general knowledge for assessing the obviousness of the claimed invention. Accordingly, the board cannot accept that the fact that document (D2) itself does not refer to single-domain antibodies would have discouraged the skilled person to solve the technical problem in an obvious manner and arrive at the claimed subject-matter.

32. The board furthermore notes that also the absence of pointers to the closest prior art in a disclosed teaching to be combined with the disclosure of the closest prior art in the assessment of inventive step, does not, as such constitute a barrier for combination of the prior art teachings by the skilled person thereby arriving in an obvious manner at the claimed subject-matter. Moreover, in the present case the board notes that document (D12), in the passage referred to by the appellant in column 5 states: "*In particular it would be desirable to introduce a second site for binding to serum components, to prolong the residence time of the domains in the serum; or for binding to molecules with effector functions, such as components of complement or receptors on the surfaces of cells.*" (emphasis added by the board). Accordingly, it

cannot fairly be argued that the absence of a hint in document (D12) to the concept disclosed in document (D2) would have discouraged the skilled person of solving the technical problem in an obvious manner as now claimed. Moreover, the board notes that the passage referred to by the appellant in document (D13) (page 295, left-hand column, lines 22 to 24) which merely suggested, in order to optimise the pharmacokinetic properties of VHH single-domain antibodies, to engineering their size or oligomeric state and was silent on the concept of SA-binding, frames in item 2.7.1 of document (D13) which has the title "*VHH as in vivo imaging agent*" in fact has no bearing on the now claimed invention. In relation to therapeutic applications their small size is rather highlighted as an advantage in each application where bispecific or multivalent antibodies are needed (see e.g. point 2.7.3.1 bridging pages 296 and 297). Accordingly, the line of argument based on the disclosure on documents (D12) and (D13) must also fail.

33. In a fourth line of argument the appellant submitted that the claimed invention offered surprising advantages as could be taken from document (D53), summarising the half-life increasing effects of the technologies disclosed in documents (D1) to (D4) and document (D48). The claimed invention resulted in *in vivo* serum half-life increases in respect of domain antibodies of 60 to 100 times, compared to the 1.4 times or 8 times as argued by the respondents, increase reported on in document (D2).

34. The board notes however (see point 27, above), that claim 1 does not make reference to any concrete ratio of increase of the serum *in vivo* half-life of the claimed dual-specific ligand. Accordingly, while the

appellant's argument might be of relevance for certain specific embodiments covered by claim 1, it cannot be taken to apply over the whole breath of the claim. Therefore, without claim 1 being limited to particular embodiments to which the argument applies, also this argument of the appellant must fail.

35. In view of the above considerations, the board concludes that the subject-matter of claim 1 of all request before it lacks inventive step. Accordingly, the appeal is to be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated