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Datasheet for the decision of 20 February 2024

Case Number: T 1019/22 - 3.3.04

Application Number: 14777078.8

Publication Number: 3049439

IPC: C07K16/28, C07K16/30

Language of the proceedings: EN

Title of invention:
Bispecific nanobodies

Patent Proprietor:
Ablynx N.V.

Opponent:
Høiberg P/S

Headword:
Bispecific nanobodies/ABLYNX

Relevant legal provisions:
EPC Art. 100(a)
RPBA 2020 Art. 11

Keyword:

Inventive step - yes
Remittal - special reasons for remittal (yes)
Obiter dictum - not part of the reasons for the decision

Decisions cited:

T 0802/97, T 0967/97, T 0473/98, T 0725/05, T 0021/08, T 0726/10, T 2238/11

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Case Number: T 1019/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 20 February 2024

Appellant: (Opponent)	Høiberg P/S Adelgade 12 1304 Copenhagen K (DK)
Representative:	Høiberg P/S Adelgade 12 1304 Copenhagen K (DK)
Respondent: (Patent Proprietor)	Ablynx N.V. Technologiepark 21 9052 Ghent-Zwijnaarde (BE)
Representative:	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 17 February 2022 rejecting the opposition filed against European patent No. 3049439 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	O. Lechner
	A. Bacchin

Summary of Facts and Submissions

I. The opponent (appellant) filed an appeal against the opposition division's decision to reject the opposition against European patent 3 049 439 as granted.

II. The patent is based on European patent application No. 14 777 078.8, published as WO 2015/044386 A1 (the "application as filed").

III. In the statement of grounds of appeal, the appellant addressed objections under Article 100(a) EPC (novelty) and Article 100(b) and (c) EPC, referencing its notice of opposition, which was attached. The appellant detailed its objections under Article 100(a) EPC specifically in relation to inventive step and also submitted new document D16.

IV. The patent proprietor (respondent) replied to the statement of grounds of appeal. The main request was for the patent as granted. Additionally, the respondent resubmitted sets of claims according to auxiliary requests 1 to 17 (first filed during the opposition proceedings).

V. Both parties provided further submissions.

VI. By letter dated 15 December 2023, the appellant withdrew its request for oral proceedings and announced it would not attend the oral proceedings.

VII. In response to the board's communication under Article 15(1) RPBA, the respondent submitted a set of claims according to auxiliary request 18.

VIII. The oral proceedings were held before the board as scheduled in the absence of the appellant, which had notified the board in writing of its non-attendance.

The appellant was treated as relying on its written case, in line with Rule 115(2) EPC and Article 15(3) RPBA.

At the end of the proceedings the Chairwoman announced the board's decision.

IX. Claim 1 of the main request (patent as granted) reads as follows:

"Polypeptide comprising a first and a second immunoglobulin single variable domain (ISV), wherein
- said first ISV binds to a first target with an average KD value of between 10 nM and 200 nM as measured by surface plasmon resonance;
- said second ISV binds to a second target with an average KD value of between 10 nM and 0.1 pM as measured by surface plasmon resonance; and

wherein said first ISV and said second ISV bind to said first target and said second target present on the surface of the same cell,
wherein said first target is different from said second target,
wherein said second ISV enhances binding of said first ISV,
wherein binding by said first ISV inhibits a function of said first target,
wherein said first target is chosen from the group consisting of Receptor Tyrosine Kinases (preferably class I), GPCRs, DDR1, Discoidin I (CD167a antigen),

DDR2, ErbB-1, C-erbB-2, FGFR-1, FGFR-3, CD135 antigen, CD117 antigen, Protein tyrosine kinase-1, c-Met, CD148 antigen, C-ret, ROR1, ROR2, Tie-1, Tie-2, CD202b antigen, TrkA, Trk-B, Trk-C, VEGFR-1, VEGFR-2, VEGFR-3, Notch receptor 1-4, FAS receptor, DR5, DR4, CD47, CX3CR1, CXCR-3, CXCR-4, CXCR-7, Chemokine binding protein 2, and CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11; and
said second target is chosen from the group consisting of carcinoembryonic antigen ("CEA"), MART-1, gp100, MAGE-1, HER-2, and Lewis^{Y} antigens, CD123, CD44, CLL-1, CD96, CD47, CD32, CXCR4, Tim-3, CD25, TAG-72, Ep-CAM, PSMA, PSA, GD2, GD3, CD4, CD5, CD19, CD20, CD22, CD33, CD36, CD45, CD52, and CD147; and Cytokine receptors including interleukin-2 receptor gamma chain (CD132 antigen); interleukin-10 receptor alpha chain (IL-10R-A); interleukin-10 receptor beta chain (IL-10R-B); interleukin-12 receptor beta-1 chain (IL-12R-beta1); interleukin-12 receptor beta-2 chain (IL-12 receptor beta-2); interleukin-13 receptor alpha-1 chain (IL-13R-alpha-1) (CD213 al antigen); interleukin-13 receptor alpha-2 chain (interleukin-13 binding protein); interleukin-17 receptor (IL-17 receptor); interleukin-17B receptor (IL-17B receptor); interleukin 21 receptor precursor (IL-21 R); interleukin-1 receptor, type I (IL-1R-1) (CD121 a); interleukin-1 receptor, type II (IL-1R-beta) (CDw121b); interleukin-1 receptor antagonist protein (IL-1ra); interleukin-2 receptor alpha chain (CD25 antigen); interleukin-2 receptor beta chain (CD122 antigen); interleukin-3 receptor alpha chain (IL-3R-alpha) (CD123 antigen)."

X. Reference is made to the following documents:

D1 : WO 2005/117973 A2

D2 : WO 2006/091209 A2

D11: Robinson M. K. et al.; Br. J. Cancer (2008); 99: 1415-1425

D15: US 8,440,192 B2

D16: Bartunek J. et al.; J. Cardiovasc. Trans. Res. (2013); 6:355-363

XI. The following terms are used:

The bispecific binding molecule as claimed comprises a first and a second immunoglobulin variable domain (ISV).
The "first ISV" as used in the patent in suit functionally corresponds to the "second binding domain" or "effector domain" as used in document D1. This domain primarily serves to inhibit (as per the patent) or modulate (as per document D1) the biological activity of a target (also termed "receptor B" in document D1), which is present on both diseased and normal (healthy) cells.

The "second ISV" as used in the patent in suit functionally corresponds to the "first binding domain" or "targeting domain" in document D1. Compared with the "first ISV", the "second ISV" should bind with higher affinity to its target (also termed "receptor A" in document D1). The second ISV is responsible for directing the bispecific binding molecule to the surface of diseased cells. Its binding to a target exclusive to diseased cells enhances the binding of the first ISV to the same cell, thereby reducing its binding to normal (healthy) cells.

XII. The appellant's arguments, where relevant to the decision, can be summarised as follows.

(a) *Objections under Article 100(a) EPC in the context of novelty and under Article 100(b) and (c) EPC*

Concerning added subject-matter, sufficiency of disclosure and novelty, reference was made to the reasons provided in the notice of opposition of 25 September 2020, which were enclosed with the statement of grounds of appeal.

(b) Inventive step - Article 100(a) in conjunction with Article 56 EPC

Closest prior art

Document D1 (or, in the alternative, document D15) as well as document D11 constituted promising starting points for assessing inventive step.

- *Document D1 or D15 as the closest prior art*

Document D1 (or, in the alternative, document D15) related to the same concept as the patent and provided bispecific binding molecules with a high-affinity binding domain to achieve specific targeting of a target cell and a low-affinity binding domain to obtain functional effects on that same target cell (paragraph [0021]). According to document D1, the bispecific molecules improve the specificity and the ability to modulate the biological activity of target cells without affecting non-target cells (paragraph [0018]).

Document D1 contained obvious errors, such as on page 3, line 15, claim 1, and other passages; however,

the skilled person would understand from the overall context, particularly paragraph [0023], that the targeting domain should have high affinity. Therefore, the terms "at least 10^{-7} M" and "at least 10 times lower" were intended to indicate a higher affinity than 10^{-7} M and should be read as "10^{-7} M or less" and "at least 10 times greater."

During examination, the EPO recognised these as obvious errors and allowed corrections for the low-affinity domain. The US Patent and Trademark Office also permitted these corrections, which were thus reflected in document D15.

The opposition division noted that while document D15 corrected the obvious errors in document D1, it introduced new inconsistencies. Therefore, the opposition division chose to base its analysis on document D1, considering it the original text, but emphasised that document D1 should be interpreted sensibly.

Difference, its technical effect, and objective technical problem to be solved

At best, the difference between document D1 and the patent could be considered to be the combined disclosure of the selection of ISVs as binding moieties for both binding domains.

Each of the differences identified by the opposition division was either disclosed in document D1 or strongly suggested by it. The opposition division, however, disregarded the general description of document D1 in its analysis, focusing only on the examples. It was crucial to consider what the document

suggested to the skilled person as a whole, rather than concentrating solely on the examples.

ISV format
Paragraph [0048] of document D1 explained that antibodies may be antibody fragments, and paragraph [0049], specifically page 17, line 14, specified that antibody fragments may be domain antibodies, i.e. immunoglobulin single variable domains (ISVs), according to the patent.

Affinities
Paragraphs [0011], [0012], [0013], [0016] and [0034], Example 7 and claim 10 of document D1 disclosed that the targeting arm of the bispecific agents may have K_Ds between 10 nM and 1 pM, i.e. within the ranges in claim 1 of the main request.

On account of the obvious error contained in document D1, paragraphs [0011], [0013], [0014], [0015] and [0034] and claim 1 should correctly be read as disclosing that the affinity of the second targeting arm is at least 10 times higher than that of the effector domain.

It was beyond doubt that document D1 disclosed that the effector arm may have a K_D that is at least 10 times higher than that of the targeting arm.

At least a K_D of the targeting arm of 10 nM in combination with a K_D of the effector arm of 100 nM or 200 nM was explicitly disclosed by document D1. All of these K_Ds fell within the ranges claimed in the patent. The claimed K_D ranges were arbitrarily selected and were not associated with a technical effect as set out in the summarising table reproduced on page 14 of the

decision under appeal (which summarises the data in Tables 4.1 and 4.4 of the patent in suit).

All the constructs tested in Example 1 of the patent fell outside the scope of the claims. Consequently, the results shown in Figure 1.8 could not be used to support a technical effect of the claimed K_D range.

Type of effectors

Although document D1 primarily addressed methods for modulating biological activities, it specified that modulation can include inhibition. For example, page 5, lines 11 to 12, disclosed a reduction in receptor tyrosine kinase activity. Page 9, lines 6 to 8, explicitly stated that modulation of a specific biological effect may involve inhibition. Additionally, page 20, lines 17 to 20, indicated that modulation can encompass the inhibition of the biological activity of the target molecule.

The objective technical problem was to provide further bispecific constructs in line with the rationale of document D1.

Obviousness

The solution provided by the patent was obvious over the disclosure of document D1 taken alone or in combination with the disclosure of document D11.

Document D1 specifically pointed to the selection of domain antibodies and also to K_Ds within the claimed ranges.

The skilled person aiming to solve the objective technical problem would have consulted document D11 and found that K_Ds within the claimed range were useful.

- *Document D11 as the closest prior art*

The appellant did not address the issues relating to the admittance of a line of argument relying on document D11 as the closest prior art, but instead presented a detailed problem-solution approach based on this document for the main request (statement of grounds of appeal) and the auxiliary requests (letter dated 22 December 2022).

XIII. The respondents' arguments, where relevant to the decision, can be summarised as follows.

(a) *Admittance of objections under Article 100(a) EPC in the context of novelty and under Article 100(b) and (c) EPC*

Regarding the grounds for opposition under Article 100(a) EPC (novelty) and Article 100(b) and (c) EPC, the appellant's statement of grounds of appeal merely referenced the notice of opposition dated 25 September 2020 without specifically contesting the opposition division's decision on these points. The appellant did not provide any reasons, facts or evidence to demonstrate why the decision was to be considered incorrect. Established case law indicated that a simple reference to earlier submissions was insufficient under Article 108 EPC and Article 12(3) RPBA. Therefore, these objections were not to be admitted.

(b) Inventive step - Article 100(a) in conjunction with Article 56 EPC

- *Document D1 as the closest prior art*

Document D1 represented the closest prior art.

Difference, its technical effect, and objective technical problem to be solved

The claimed subject-matter differed from the disclosure in document D1 on account of the following features:
- the type of binding moiety (two diabodies or scFVs in document D1 versus two ISVs in the claims),
- the combination of selected K_D ranges for the first and second binding moieties (very broad in document D1 versus a specific selection in the claims), and
- the type of effectors ("modulators" in D1 versus "inhibitors" in the claims).

The appellant had failed to address key aspects of the opposition division's decision, in particular that the claimed subject-matter was a selection invention in view of document D1 (point 9.8 of the decision under appeal).

ISV format
An arbitrary double selection from a list of a certain length was required from paragraph [0049] of document D1 to arrive at constructs in which both binding moieties were "domain antibodies". Document D1 did not disclose any bispecific constructs comprising two ISVs as claimed.

Affinities
The broadest affinity ranges in document D1 included a K_D of 100 nM for the targeting arm and an affinity that was at least 10 times weaker, i.e. 1000 nM or weaker, for the effector arm (claim 1; paragraphs [0011] to [0016]);
however, document D1 did not disclose or suggest a combination of a K_D for the targeting arm with a K_D for the effector arm that was 10 times greater; instead, paragraph [0190] emphasised a much greater K_D difference, preferring differences of "*100 times or more*", as noted in paragraph [0023]. There was no direct or clear disclosure in paragraph [0011] or elsewhere in document D1 of a K_D range of "20 pM to 200 nM" for the effector arm, nor any specific K_D values within this range. The only way to obtain K_D values for the effector arm within the claimed narrow range would have been to make an arbitrary selection of K_D for the targeting arm combined with a non-preferred multiple of the difference in K_D for the effector arm.

Type of effectors
In document D1 (pages 9, lines 6 to 8, and page 20, lines 17 to 20), "modulate" and "modulation" are defined as encompassing either increasing or inhibiting biological activity, with no preference indicated for inhibition. Furthermore, paragraphs [0020], [0041], [0042] and [0059], as well as page 5, lines 11 to 12, of document D1 also presented increasing and inhibiting activity as equal alternatives. Therefore, a specific selection was required to arrive at a bispecific construct with an effector arm with inhibitory activity.

Document D1 relied solely on *in silico* modelling, which inaccurately predicted that bispecific binders with

varying affinities would have similar IC50 values (points 9.5 and 9.9 of the decision under appeal); however, experimental data from the patent (Table 4.4) demonstrated that these predictions were incorrect; bispecific constructs with different affinities did not achieve the expected IC50 improvements (paragraphs [0298] and [0299]).

The technical promise in document D1 that weakly binding effectors could achieve high efficacy was not realised. In contrast, the patent demonstrated that constructs with specific K_D ranges provided improved potency and selectivity compared with those predicted by document D1 (points 9.5 and 9.7 of the decision under appeal). The patent demonstrated that constructs within the claimed affinity range significantly outperformed those predicted by document D1, offering a notable therapeutic advantage (e.g. Example 1 and Figure 4.5 of the patent).

Therefore, the purposive selection of upper and lower K_D limits led to effective bispecific constructs, contrary to the predictions made in document D1.

In agreement with the decision under appeal, the objective technical problem was to find concrete conditions where a bispecific construct along the lines of document D1 and based on ISVs actually worked to some reasonable degree of potency and selectivity.

Obviousness

The claimed subject-matter was a "selection invention" over the disclosure of document D1 for the reasons provided by the opposition division in the decision under appeal.

It was not obvious to adapt the method disclosed in document D1, which focused on scFvs, for ISVs or to translate the scFv-associated affinity ranges to effective ranges for ISVs.

Moreover, document D11, which concerned a bispecific scFv targeting a single effector, i.e. the ErbB2 and ErbB3 heterodimer, lacked guidance on applying these concepts to ISVs of different affinity ranges, making such adaptations non-trivial.

Third, the prediction model in document D1 with regard to bispecific scFvs in paragraph [0190] was incorrect, at least with regard to ISVs. The predicted improvement in document D1 was simply not there. The selection of ISVs with the claimed K_D values was not the result of an arbitrary selection since it resulted in a recognisable technical effect.

Therefore, a purposive selection of affinity ranges was required to arrive at the claimed invention, which would not have been suggested by document D1 alone, indicating a non-obvious technical effect (points 9.7 and 9.8 of the decision under appeal).

Even if considered, document D11 did not provide specific guidance on ISVs or affinities as claimed, and its concept of "moderate- to low-affinity" arms diverged from the differential K_Ds required (document D11, page 1423). Moreover, document D1 explicitly excluded ErbB2 and ErbB3 from being paired as targets, making the combination with document D11 unlikely (document D1, claims 1, 12, 24, 34, 43 and 51).

Consequently, there was no clear incentive or expectation of success to arrive at the claimed invention without exercising inventive skill when based on the disclosure in documents D1 and D11.

- *Document D15 as the closest prior art*

The opposition division rejected document D15 as the closest prior art. The appellant did not give any reasons why this decision was wrong. Therefore, an objection starting from document D15 as the closest prior art had not been validly raised in appeal. The appellant could not simply introduce such an attack by alleging that the arguments for document D1 applied *mutatis mutandis*.

- *Admittance of document D11 as the closest prior art*

In the opposition proceedings, document D11 was primarily cited against novelty for claims 1 to 3, 5 to 7 and 11 to 15. It was only used as a secondary document in the inventive step analysis for claim 1, with document D1 being considered the closest prior art. Throughout the written opposition proceedings there was only one half-sentence mentioning document D11 as the prior art potentially closest to the subject-matter of claims 8 to 10 (see notice of opposition page 15, last paragraph). It had never been presented as the prior art document closest to the subject-matter of claim 1.

During the oral proceedings before the opposition division, the discussion focused on the inventive step starting from document D1 or D15 as the closest prior art. Only at the very end of the discussion did the appellant attempt to use document D11 as an alternative

closest prior art document against the subject-matter of claim 1. The opposition division refused to consider document D11, as it was introduced too late, and the chairperson stopped any further discussion of this matter. This was clearly a procedural decision by the opposition division, and there was no further discussion of that matter.

However, in the decision under appeal, the opposition division did not mention its procedural decision not to admit the line of argument starting from document D11 as the closest prior art because it was introduced too late. Despite this, the decision addressed the suitability of document D11 in section 9.3.3 and provided an opinion on its inventive step in an *obiter dictum* in section 9.10. These points were not discussed during the oral proceedings. Neither the findings in point 9.3.3 nor those in point 9.10 had been part of the discussion between the parties during the oral proceedings.

To the respondent's disadvantage, the appellant introduced an inventive step argument based on document D11 as the closest prior art in the statement of grounds of appeal. This new argument required the inventive step to be completely re-evaluated, significantly impacting the respondent's rights.

In the statement of grounds of appeal (see the first half of page 2/18), the appellant acknowledged that the technical effect linked to the selection between ISV and scFv formats had not been discussed during the oral proceedings before the opposition division.

The appellant did not request that the opposition division's decision not to admit document D11 as the closest prior art be overturned.

XIV. The parties' relevant requests for the decision were as follows:

(a) The appellant (opponent) requested in writing that
- the decision under appeal be set aside, and that the patent be revoked;
- document D16 be admitted into the proceedings.

(b) The respondent (patent proprietor) requested that
- the appeal be dismissed and the opposition division's decision to reject the opposition be upheld;
- the grounds of opposition under Article 100(a) EPC in conjunction with Article 54 EPC, Article 100(b) and (c) EPC not be admitted into the appeal proceedings for lack of substantiation on appeal;
- the appellant's new inventive step attack under Articles 100(a) and 56 EPC starting with document D11 as closest prior art not be admitted into the appeal proceedings and that document D16 not be admitted as well;
- the case be remitted to the opposition division for evaluation of the new technical case raised for the first time by the board against the technical effect being present over the breadth of the claims;
- should the board not be minded to remit, an adjournment of the oral proceedings to provide the respondent sufficient time to present its defence on the board’s new case;
- that auxiliary request 18 be admitted;

- the case be remitted to the opposition division for discussion of auxiliary requests 1 to 18 or alternatively that the patent by maintained by the board on the basis of any of these, with auxiliary requests 1 and 14 to 17 as filed on 18 February 2021; auxiliary requests 1 to 5 and auxiliary requests 2 to 13 as filed on 7 December 2021; auxiliary request 18 as filed on 9 February 2024.

Reasons for the Decision

1. The appellant did not attend the oral proceedings but maintained its written submissions. It had notified the board in writing of its non-attendance. The appellant was treated as relying on its written case, in line with Rule 115(2) EPC and Article 15(3) RPBA.

Admittance of objections under Article 100(a) EPC in the context of novelty and under Article 100(b) and (c) EPC

2. In the statement of grounds of appeal the appellant referred to the notice of opposition (which was attached to the statement of grounds of appeal) with respect to its objections under Article 100(a) EPC in the context of novelty as well as under Article 100(b) and (c) EPC.

In view of the primary object of the appeal proceedings being to review the decision under appeal in a judicial manner, general references to submissions from opposition proceedings, even if copies of the relevant submissions are annexed to a letter in appeal proceedings, cannot replace a dedicated argument tailored to the grounds for the decision, as required by Article 12(2) RPBA. They are also critical in view

of the substantiation requirements set out in Article 12(3) RPBA, according to which parties must submit their complete case in the statement of grounds of appeal or in the reply to it, to allow the board and the other parties to understand why the contested decision should be reversed without having to make any further investigations of their own (see Case Law of the Board of Appeal of the European Patent Office, 10th edition, 2022, V.A.3.2.1 and 3.2.2). All the letters from the opposition proceedings are accessible from the file anyway; therefore, attaching letters from the opposition proceedings and making general references to them does not fulfil this requirement.

3. No further substantiation has been provided that specifically addresses the opposition division's reasoning in the decision under appeal on these issues. Therefore, the appellant's submissions with regard to these objections cannot be considered to satisfy the requirements of Article 12(3) RPBA. Therefore, pursuant to Article 12(5) RPBA, the board decided not to admit the objections of lack of novelty, lack of sufficiency and added subject-matter in respect of the set of claims in the main request.

Claim construction

4. Claim 1 of the main request is a product claim directed to an at least bispecific polypeptide comprising an ISV targeting a first antigen with a dissociation constant (K_D) of 10 to 200 nM and another ISV targeting a second target with a K_D of 10 nM to 0.1 pM. The two targets are not the same but need to be expressed on the surface of the same cell. Binding of the higher-affinity second ISV to the second target enhances the binding to the lower-affinity first ISV to its first

target. Upon binding, the first ISV inhibits a function of the first target.
Lists of specific target molecules for the first and second ISVs are defined.

According to the claim language the affinities of the two ISVs for the two different targets may be identical (i.e. 10 nM) or differ by a factor of up to $2x10^6$ (i.e. 200 nM vs. 0.1 pM); however, there is also the functional requirement that the second (targeting) ISV enhances the binding of the first (effector) ISV, which excludes the situation in which two ISVs are used that do not result in the binding of the first ISV being enhanced.

5. In this context it is important to note that a "lower affinity" corresponds to a higher dissociation constant (K_D) value, while a "higher affinity" corresponds to a lower K_D value, because K_D inversely reflects the strength of binding between two molecules.

6. The term "immunoglobulin single variable domain" (ISV) encompasses any (single) domain antibody (dAb) with an immunoglobulin-like structure, including "VHHs"/"nanobodies".

Inventive step - Articles 100(a) and 56 EPC

Closest prior art

7. Documents D1, D15 and D11 were indicated as suitable starting points for assessing inventive step.

8. Document D15 is a divisional application of document D1 in the United States national phase. The teaching of the two documents is virtually identical. Some of the

contradictions in document D1 (see below) have been resolved in document D15, but there remains a contradiction in the teaching as to which of the two binders must have the higher affinity, i.e. the lower K_D (see document D15, column 2, lines 41 to 51).

9. On purely precautionary grounds, given that the inconsistencies in document D15 were arguably even more serious than in document D1, and since document D1 is the original text, the opposition division decided to choose the lesser of two evils. D1 was taken as the closest prior art. The findings on inventive step were in any event based on the sections of document D1 that were not changed in document D15.

10. In view of the above the board considers that document D15 was part of the decision under appeal and that, given the circumstances, the appellant has addressed document D15 in the statement of grounds of appeal in a reasonable manner. Therefore, the inventive step reasoning based on document D15 is admissible.

Document D1 as the closest prior art

11. Document D1 discloses bispecific binding agents (bsBAs) with an improved ability to bind to target cells without binding to non-target cells with the aim of increasing or decreasing the biological activity of a target molecule on the target cell and thereby providing an improved ability to modulate biological activity of target cells with reduced, if any, effect on the corresponding activity of non-target cells. The specificity of targeting diseased cells by the bispecific binding agents can be increased by controlling the differences in the binding affinities of the two binding domains of the bsBAs (see paragraphs

[0017] and [0018]). Paragraph [0043] explains that the use of bsBAs with a single high-affinity binding domain is sufficient to provide specific binding to cells of interest. According to paragraph [0056] the term "binding agent" may include antibodies, antibody fragments, aptamers, peptides, antibody mimetics or also a natural ligand for a receptor. Paragraphs [0049], [0067] and [0070] define "antibody fragments" and "univalent binding agent" as encompassing e.g. Fab, Fab', $F(ab')_2$, Fv, etc., or single domain antibodies. According to paragraph [0090] the affinities of the binding domains of the bsBA are determined after the bsBA is formed so that the relative affinity of the binding domains can be determined.
Document D1 provides *in silico*-based predictions, but no *in vitro* or *in vivo* experimental results.

It is noted that document D1 provides technically correct definitions for "affinity" and the associated "dissociation constant (K_D)" in paragraphs [0047] and [0065].

11.1 However, the teaching in document D1 is contradictory as far as the affinity distribution between the two binding domains is concerned, to such an extent that the skilled person would not have derived clear teaching of whether the targeting domain or the domain which is to inhibit the biological activity is to have a higher binding affinity (i.e. a lower K_D value).

Paragraphs [0014], [0023] and [0026] to [0028] disclose that a higher-affinity (i.e. a lower K_D value) second (targeting) domain targeted to receptor A (present on tumour cells) and a lower-affinity (i.e. a higher K_D value) first (effector) domain targeted to receptor B (also present on non-tumour cells), and having an

affinity that is 5, 10, 20, 30, or even 100 or more times higher for receptor A than for receptor B, will preferentially bind to the cancer cells, and by normal kinetic interactions, will bind in larger numbers to the cancer cells as compared with normal cells.

11.2 Claims 1, 11 and 24 of document D1 require exactly the opposite affinity distribution, i.e. the first binding domain has to bind to the first target molecule (the tumour antigen) with a K_D of at least 100 nM or greater, and the second (effector) binding domain binds to the second target molecule (also expressed on normal cells) with an at least 10- or 20-times lower affinity, which can be calculated to correspond to a $K_D \geq 1$ µM, than the K_D of said first binding domain.

A corresponding disclosure can also be found in paragraphs [0011] to [0013], [0015] or [0016] of document D1. Paragraph [0011], for example, discloses a bispecific binding agent having a first binding domain having a K_D between 10^{-8} to 10^{-12} M, i.e. 10 nM to 1 pM, for the first target molecule and a second binding domain (targeting the molecule with biological activity) having a K_D for the second target molecule that is at least 20 times lower than the K_D of the first binding domain and can be calculated to correspond to a K_D between 500 pM to 0.05 pM, which represents a higher relative affinity (see page 4, lines 9 to 12).

11.3 Furthermore, dependent claim 10 is also inconsistent with the teaching of its independent claim 1 in that it requires the first (tumour-cell-specific) binding domain to have a K_D in the range between 10^{-8} and 10^{-12} M, i.e. 10 nM to 1 pM, which is inconsistent with the

at least 10^{-7} M, i.e. 100 nM, or greater required by independent claim 1.

11.4 The computational modelling in document D1 predicts that, in the bispecific construct having a first (targeting) domain with an affinity of K_D = 1 nM, the second (effector) domain with 1 µM affinity would be "as effective" as an effector domain that binds with a K_D = 1 nM affinity (see paragraph [0190]).

Difference, its technical effect, and objective technical problem

12. The subject-matter of claim 1 differs from the teaching in claim 1 of document D1 in that

(a) it specifically utilises a bispecific polypeptide comprising two ISVs as binding arms;

(b) the second (targeting) ISV binds with an affinity defined by a K_D in the range between 10 nM and 0.1 pM and the first (effector) ISV binds with an affinity defined by a K_D in the range between 10 nM and 200 nM, i.e. with an affinity that is between equal to and up to $2x10^7$ times weaker compared with the second (targeting) ISV, wherein said second (targeting) ISV has to enhance the binding of the first (effector) ISV;

(c) the effector first ISV inhibits the function of its target; and

(d) on account of the list of targets selected for the targeting second ISV and the effector first ISV.

13. The patent provides different examples demonstrating that the claimed concept of using a second (targeting) ISV with higher affinity to enhance the binding of the first (effector) ISV with lower affinity, with both targets being present on the same cell, works (see e.g.

Tables 4.1 and 4.4 (summarised in Annex 1 as attached to the respondent's reply to the statement of grounds of appeal) and Figure 4.5).
The functional requirement that the second ISV must enhance the binding of the first ISV rules out situations in which two ISVs are used that do not result in the binding of the first ISV being enhanced.

14. The objective technical problem in the decision under appeal was defined as "[...] *to find concrete conditions where a bispecific construct along the lines of D1 and based on ISVs actually works to some reasonable degree of potency and selectivity.*"

15. Based on the parties' arguments and the analysis above, the board finds it necessary to reformulate the objective technical problem.

The phrase "actually works to some reasonable degree of potency and selectivity" has been reformulated to read "allow for a preferential and enhanced inhibition..." to avoid reference to the closest prior art in the objective technical problem.

Cells that express the first and second target antigens are already part of the disclosure in the closest prior art and therefore need to be included in the objective technical problem.

Given difference (a) (see point 12. above), it is inappropriate to incorporate an element of the solution — specifically, the use of ISVs — into the objective technical problem. Consequently, it was necessary to formulate this aspect more generally.

16. Therefore, the objective technical problem is to provide constructs that allow for a preferential and enhanced inhibition of the function of a first target molecule only on cells that express both the first and second target antigens.

17. The solution is as defined in claim 1.

Obviousness - starting from document D1 alone

18. Starting from the bispecific binding agent in claim 1, in document D1 several selections are necessary to arrive at the claimed subject-matter.

ISV format

18.1 Document D1 exemplifies bispecific binding agents as being constructs containing two scFvs ((scFv)2 and diabodies; Example 1). To arrive at the ISV-antibody format for both the targeting and effector domains, a two-step selection is needed based on the options outlined in paragraphs [0049] and [0067] of document D1 for the binding-agent format of the first and second binding domain; however, document D1 provides no specific guidance for making this selection.

Affinities

19. Due to the contradictory teaching in document D1 regarding the affinity distribution between the two binding domains (see points 11.1 to 11.3 above), a skilled person would only understand that a certain affinity difference is necessary between the targeting and effector domains, but would not know which domain should bind its target structure with higher affinity.

20. However, even if the contradictory passages regarding the affinity differences were read in favour of the appellant — the targeting domain binding with higher affinity than the effector domain — document D1 provides no clear guidance in the direction of the claimed affinity ranges.

20.1 Document D1 defines, for the first (targeting) domain, an affinity of at least 100 nM (see e.g. claim 1; paragraph [0011]) or a range between 10 nM and 1 pM (see e.g. claim 10; paragraphs [0011] and [0034]), and, for the second (effector) domain, an upwardly open affinity difference of at least 10 times, 15 times, 20 times, etc. (see point 11.1 above). The only disclosure of a concrete affinity combination can be found in Example 6 in paragraph [0190], in which the targeting domain has an affinity of K_D = 1 nM and the effector domain has an affinity of K_D = 1 µM. A K_D of 100 nM for the targeting domain and a K_D of 1 µM are outside the ranges in claim 1 of the main request, i.e. 10 nM to 0.1 pM for the targeting ISV and 10 nM to 200 nM for the effector ISV.

20.2 With reference to Table 4.4 in the patent in suit (summarised in Annex 1 as provided in the now respondent's response to the notice of opposition), the appellant argued that the data in the patent in suit did not support a clear distinction in potency or selectivity for the claimed bispecific constructs compared with those disclosed in document D1. Therefore, there was no unexpected technical improvement over the disclosure in document D1.

20.3 However, document D1 first does not disclose or point to the specific combination of affinity ranges for the effector ISV (K_D = 10 to 200 nM) and targeting ISV (K_D

= 10 nM to 0.1 pM) as claimed, not even in the *in silico* simulations in the examples (see point 20.1 above). A selection is thus required to arrive at the claimed affinity ranges.

Second, and contrary to the lack of any experimental evidence in document D1, Table 4.4 and Figures 4.4 and 4.5 of the patent in suit show that using bispecific constructs as claimed results in dose-dependent increased binding to and a potency shift in the inhibition of EGFR phosphorylation in EGFR+/CEA+ double positive Lovo cells compared with EGFR+/CEA- HER14 cells.

Type of effectors

21. A further selection needs to be made regarding the activity of the effector domain. While document D1 refers to the modulation of a biological activity, i.e. increasing or inhibiting the biological activity, without preference for one of the two options (paragraphs [0019] or [0061]), the claimed effector ISV has to inhibit a function of its target.

Lists of targets

22. The list of targets selected for the targeting second ISV and the effector first ISV in claim 1 differs from those in claims 5 to 9 of document D1 for the first (targeting) and second (effector) binding domains. While some targets, such as CEA, MART-1, MAGE-1, Lewis Y, Her2 (ErbB2), EpCAM, and PSMA for the targeting domain, and receptor tyrosine kinases (e.g., ErbB3, ErbB4), FGFR-1, and FGFR-3 for the effector domain, are identical to those in claim 1 of the main request,

claim 1 also lists several alternative targets for both domains that are not mentioned in document D1. Consequently, at least formally, further selections must be made in order to arrive at the lists of targets for the effector and the target domain as claimed.

23. In summary, multiple selections, at least for the antibody format used for each of the targeting and the effector domain, their affinities, and the type of effectors are necessary to arrive at the claimed subject-matter. In the absence of any pointer in document D1 to the claimed combination of features, a skilled person would not have arrived at the subject-matter of claim 1 in an obvious way. Therefore, the subject-matter of claim 1 is considered to involve an inventive step in view of the teaching within document D1.

Obviousness - combination of document D1 and D11

24. The board also considers that a skilled person would not have been motivated to combine the teaching of document D1 with that of document D11.

25. Document D11 shows that co-targeting the preferred ErbB2/ErbB3 heterodimer with a bispecific construct comprising two scFvs promotes increased targeting selectivity over antibodies specific for one of the two tumour-associated antigens (TAA) alone. This bispecific construct, comprising scFvs that bind ErbB3 and ErbB2, respectively, exhibits selective targeting of tumour cells *in vitro* and *in vivo* co-expressing both antigens, compared with tumour cells expressing only one antigen or normal cells expressing low levels of both antigens {see e.g. title and abstract). The ErbB3 binding arm has an affinity of K_D = 160 nM, while the K_D of the

ErbB2 binding arm is 1 nM (see page 1418, left-hand column, paragraph 2). Fusing the two scFvs into the bispecific format does not dramatically alter the K_Ds of the individual scFv (see page 1418, right-hand column, paragraph 1). *In vitro* tests demonstrate that the bispecific scFv construct has intrinsic anti-cancer activity, which is mediated by the anti-ErbB3 arm (see abstract).

26. The teaching of document D11 differs from the subject-matter of claim 1 in that an ErbB2xErbB3 receptor heterodimer is targeted as a single "effector" target, rather than using a separate anchor. The improved selectivity observed in document D11 is not based on quantitative factors, such as avoiding off-target effects through differential K_D values. Document D11 also fails to disclose bispecific ISV constructs.

27. Therefore, the subject-matter of claim 1 is not obvious when considering a combination of the teaching of document D1 and document D11, either.

Document D15

28. In view of the considerations in point 8. above, starting from document D15 as the closest prior art, the subject-matter of the main request does not involve an inventive step for the same reasons, *mutatis mutandis*, as given in points 18. to 27. above.

Admittance of the line of argument starting from document D11 as the closest prior art

29. The respondent objected to the admittance of the additional line of attack of lack of inventive step of

the subject-matter of claim 1 starting from D11 as the closest prior art.

It was submitted that this attack was presented for the first time at the very end of the oral proceedings in opposition.

30. The board agrees with the respondent's view that admittance of the objection of lack of inventive step starting from document D11 as the closest prior art is indeed still an open issue in the present case.

30.1 The line of argument starting from D11 as the closest prior art was brought up again in the statement of grounds of appeal, in which the appellant provided full inventive step reasoning against claim 1 of the main request starting from document D1/D15 or D11 as the closest prior art. The same objections were maintained against some of the auxiliary requests with the appellant's submissions of 22 December 2022; however, none of these submissions addressed the procedural aspect of admitting the inventive step argument based on document D11 as the closest prior art.

30.2 During the written opposition proceedings, claim 1 was attacked in view of document D11 only for novelty and inventive step, with document D11 being treated as a secondary document. Document D11 was merely mentioned as the closest prior art for an inventive step attack against claims 8 to 10 (see page 15, last paragraph of the notice of opposition: "*Similar arguments for lack of inventive step of claim 8 to 10 can be made using D2, D3 or D11 as starting point*").

30.3 Despite the opposition division's preliminary opinion, which concluded that document D11 could not be

considered the closest prior art due to its different purpose (see page 18), the opponent's subsequent written submissions still discussed inventive step for claim 1 only based on documents D1, D2 or D15, but not document D11.

30.4 During the oral proceedings in opposition, at the very end of the discussion of inventive step, after the relevant decision on inventive step starting from document D1/D15 had been announced, the appellant brought up an objection of lack of inventive step starting from document D11 as an alternative closest prior art document against the subject-matter of claim 1.

30.5 Both the decision under appeal and the minutes of the oral proceedings before the opposition division fail to indicate whether a procedural decision was taken on the admittance of the line of argument under inventive step starting from document D11 as the closest prior art.

30.6 The minutes just mention that "*The opposition division asked both parties which document they consider the closest prior art. D11 was not brought forward as potential closest prior art at that time. The discussion of which document is the closest prior art has become final as the opposition division has already decided that D1 is the closest prior art*" (see page 4, last paragraph).

30.7 In point 9.3.3 of the decision under appeal, the opposition division stated that "*Aside from procedural issues which could make such a request inadmissible, the Division finds that in any event D11 does not provide a suitable "springboard" for arriving at the invention claimed in the opposed patent*."

In the subsequent paragraphs of point 9.3.3 of the decision under appeal, the opposition division analysed the disclosure of document D11 as the closest prior art and concluded that document D1 "*is closer than D11 in terms of relevance*".

31. These passages from the minutes and the decision make no mention whatsoever of whether the parties were heard on the admittance of this line of attack and on the substantive inventive step issues starting from document D11 as the closest prior art for claim 1.

31.1 At the oral proceedings before the board the respondent submitted that the appealed decision mixed up issues which had been discussed with those which had not. The respondent had not been heard on D11 for the question of inventive step, nor could it appeal the decision on those points as it was not negatively affected. It could have requested a correction of the minutes, but it did not.

31.2 On the other hand, by not participating in the oral proceedings, the appellant did not make any contribution to reconstructing the discussion before the opposition division. It is therefore not possible for the board to draw a final conclusion on whether the considerations made by the opposition division in the cited passages were based on any of the parties' submissions.

32. The decision under appeal also contains an *obiter dictum* in point 9.10, which does not provide further clarification in this respect. To the contrary, it creates uncertainty as to whether the question of inventive step had been conclusively decided upon.

32.1 In this section the opposition division mentioned that document D11 was not the closest prior art, and thus it would not be necessary to decide on its basis. For the sake of completeness, however, and at the request of the opponent, an assessment of inventive step had also been provided on the basis of document D11. In that assessment, the opposition division found that the subject-matter of claim 1 was inventive over the disclosure of document D11.

32.2 No mention is made of whether the line of argument starting from document D11 as the closest prior art had been admitted into the proceedings, a fact which was brought into question by the opposition division in the previous point 9.3.3 of the decision. It is even less clear whether the parties were heard on the admittance and the substance of inventive step based on document D11.

33. The board finds that the use of an *obiter dictum* was not correct in the present circumstances.

33.1 An *obiter dictum* is any general statement, either implicit or explicit, in a decision which does not constitute a *ratio decidendi* of said decision.

33.2 Accordingly, in decisions of the boards of appeal it was stated that observations in an *obiter dictum* do not, by definition, form part of a decision (see T 802/97, point 3 of the Reasons; T 2238/11, point 5 of the Reasons) and that *obiter dicta* are sometimes included in decisions of the examining and opposition divisions in order to avoid remittal (see decision T 473/98, Headnote I).

33.3 Form a purely legal point of view *obiter dicta* have no significance for the decision of the specific case and have no binding force. They normally deal with issues that were not raised in the proceedings as a whole, or on which a decision does not actually have to be made.

33.4 Accordingly, if a legal opinion expressed as an *obiter dictum* has no influence on the legal dispute, it cannot, by itself, constitute an infringement of one party's rights.

33.5 In particular, as a party's right to be heard pursuant to Article 113(1) EPC is satisfied if it has had an opportunity to present its comments on all grounds or evidence on which a decision is based, this right is not violated if a party did not have the opportunity to comment on observations in an *obiter dictum* (cf. e.g. T 726/10, point 9 of the Reasons and T 725/05, point 6 of the Reasons).

33.6 The requirements of Article 113(1) EPC are instead contravened if the decision is subsequently based on an "omitted" ground which is contained in an *obiter dictum*.

34. On account of these considerations of principle, it is apparent that the use of an *obiter dictum* in the present case was not appropriate, at least owing to the fact that it contained a part of the finding on which the decision was based, namely that the claimed subject-matter was considered inventive. Both the decision and the *obiter dictum* related to the same ground for opposition, lack of inventive step, and therefore the statement contained in the *obiter dictum* had been "omitted" from the formal decision.

34.1 After having decided that the subject-matter of claim 1 was inventive starting from document D1, the opposition division should have addressed further objections of lack of inventive step, if any were on file. Therefore, the opposition division should first have taken a decision on the admittance of the inventive step attack starting from document D11. Only if admitted, it should have then fully decided upon inventive step by also taking into account document D11 as the closest prior art after having heard both parties. Had the opposition division formally decided not to admit the attack based on document D11, there would have been no need for an *obiter dictum*.

34.2 In this context the board also notes that in cases in which the skilled person has a choice of several workable routes, i.e. routes starting from different documents, which might lead to the invention, the rationale of the problem-solution approach requires that the invention be assessed relative to all these possible routes, before an inventive step could be acknowledged (see e.g. T 967/97, point 3.2 of the Reasons and T 21/08, point 1.2.3 of the Reasons).

35. Therefore, for this reason too, the inclusion of an *obiter dictum* in the decision to deal with the question of inventive step starting from document D11 creates uncertainty as to whether the case was actually fully decided at that stage.

35.1 This legal uncertainty is confirmed by the fact that the respondent felt that an attack which should not have been admitted into the proceedings was apparently introduced by means of an "*obiter*". Legal uncertainty is also confirmed by the fact that the appellant felt the need to file additional evidence, namely document

D16, to support the objection of lack of inventive step starting from document D11 with its statement of grounds of appeal. A genuine *obiter dictum* does not make it necessary to file additional evidence.

36. The board has therefore come to the conclusion that it is not possible to infer from all of the procedural documents forming part of the opposition proceedings that document D11 as the closest prior art was not in the proceedings. Therefore, the line of argument concerning inventive step starting from document D11 is admitted.

37. However, the discussion in the opposition proceedings of document D11 as the closest prior art does not appear to have been complete and the board cannot ascertain that both parties have been heard on the substance of this issue.

The assessment of inventive step therefore seems to require further discussion.

In accordance with Article 111(1) EPC, it is left to the board to decide whether to exercise the competence of the department which was responsible for the appealed decision or to remit the case to that department for further prosecution.

The board considers that, on their own, the facts of the case would favour remittal to the opposition division for further prosecution of document D11 as the closest prior art, in particular as it would allow the respondent to argue its case in this respect. The respondent did not object to the remittal, either. It is therefore decided that the case be remitted for

further prosecution. A separate decision by the board on the admittance of document D16 is not required.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division for further prosecution.

The Registrar: The Chairwoman:

A. Vottner M. Pregetter

Decision electronically authenticated

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1019/22 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 29 November 2024
correcting an error in the decision
of 20 February 2024

Appellant: (Opponent)	Høiberg P/S Adelgade 12 1304 Copenhagen K (DK)
Representative:	Høiberg P/S Adelgade 12 1304 Copenhagen K (DK)
Respondent: (Patent Proprietor)	Ablynx N.V. Technologiepark 21 9052 Ghent-Zwijnaarde (BE)
Representative:	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 17 February 2022 rejecting the opposition filed against European patent No. 3049439 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman: M. Pregetter
Members: O. Lechner
A. Bacchin

Point 28 of the reasons for the decision T 1019/22-3.3.0.4 of 20 February 2024 states (emphasis added to identify the presence of a clerical error):

"Document 15

28. In view of the considerations in point 8. above, starting from document D15 as the closest prior art, the subject-matter of the main request does not involve an inventive step for the same reasons, *mutatis mutandis*, as given in points 18. to 27. above."

Pursuant to Rule 140 EPC, point 28 of the reasons is corrected to read as follows (emphasis added to identify the correction):

"Document 15

28. In view of the considerations in point 8. above, starting from document D15 as the closest prior art, the subject-matter of the main request does involve an inventive step for the same reasons, *mutatis mutandis*, as given in points 18. to 27. above."

The Registrar: The Chairwoman:

A. Vottner M. Pregetter

Decision electronically authenticated