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Datasheet for the decision of 4 April 2019

Case Number: T 0937/15 - 3.3.04

Application Number: 09001632.0

Publication Number: 2072045

IPC: A61K39/395, C07K16/28

Language of the proceedings: EN

Title of invention:
Antibody having a T-cell receptor-like specificity, yet higher affinity, and the use of same in the detection and treatment of cancer, viral infection and autoimmune disease

Patent Proprietor:
Technion Research & Development Foundation Ltd.

Opponents:
Schlich, George
Brunner, John Michael Owen
Strawman Limited (opposition withdrawn)

Headword:
Antibody having a TCR-like specificity/TECHNION

Relevant legal provisions:
EPC Art. 100(c), 123(2), 123(3)
EPC R. 115(2)
RPBA Art. 15(3)

Keyword:
Main request, auxiliary requests I to VII: amendments - extension of subject-matter (yes)
Auxiliary requests VIII and IX: amendements - extension of scope (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 0937/15 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 4 April 2019

Appellant: (Opponent 2)	Brunner, John Michael Owen Carpmaels & Ransford One Southampton Row London WC1B 5HA (GB)
Representative:	Brunner, John Michael Owen Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Patent Proprietor)	Technion Research & Development Foundation Ltd. Senate House Technion City 32000 Haifa (IL)
Representative:	Cabinet Plasseraud 235 Cours Lafayette 69006 Lyon (FR)
Party as of right (Opponent 1)	Schlich, George Schlich LLP 9 St Catherine's Road Littlehampton West Sussex BN17 5HS (GB)
Representative:	Schlich, George Schlich

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 26 March 2015 rejecting the oppositions filed against European patent No. 2072045 pursuant to Article 101(2) EPC**

Composition of the Board:

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

Summary of Facts and Submissions

I. Appeals were lodged by opponent 1 (appellant I) and opponent 2 (appellant II) against the decision of the opposition division to reject the oppositions against European patent No. 2 072 045.

II. The patent in suit, entitled "*Antibody having a T-cell receptor-like specificity, yet higher affinity, and the use of same in the detection and treatment of cancer, viral infection and autoimmune disease*", was granted in respect of European patent application No. 09 001 632.0 ("application as filed"), which is a divisional application of European patent application No. 03 706 876.4, which was filed under the PCT as PCT/IL03/00105, published as WO 03/068201 (document D24 in the present proceedings; "earlier application as filed").

Claim 1 as granted reads:

"1. An isolated antibody specifically bindable with a binding affinity below 10 nanomolar to a human major histocompatibility complex (MHC) class I being complexed with a HLA-restricted antigen, wherein said antibody does not bind said human MHC class I in the absence of said HLA-restricted antigen, wherein said antibody does not bind said HLA-restricted antigen in the absence of said human MHC class I."

III. Three oppositions were filed against the patent. As grounds for opposition the opponents invoked Article 100(a) EPC, on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and Article 100(b) and (c) EPC.

IV. The opposition division decided that none of the grounds for opposition prejudiced the maintenance of the patent as granted and thus rejected the oppositions.

V. Opponent 3 withdrew its opposition during the appeal proceedings.

VI. With its statement of the grounds of appeal, appellant I presented arguments as regards lack of sufficiency of disclosure, lack of novelty and lack of inventive step of the subject-matter of claim 1 as granted. No submissions were made in respect of added subject-matter.

VII. With its statement of the grounds of appeal, appellant II presented arguments as regards added subject-matter of claim 1 as granted and of claim 1 of auxiliary requests I to III, these requests having been filed during the opposition proceedings with a letter dated 27 December 2013.

VIII. In reply to the statements of the grounds of appeal, the patent proprietor (respondent) maintained the main request on which the decision under appeal was based (patent as granted), as its main request, and the set of claims of auxiliary requests I to III, and additionally filed sets of claims of auxiliary requests IV to IX, with auxiliary requests VIII and IX corresponding to auxiliary requests IV and V that had been filed with a letter dated 28 November 2014 during the opposition proceedings.

The respondent presented arguments as to why the subject-matter of claim 1 of the main request and of auxiliary requests I to VII did not contain added

subject-matter. Further, by reference to written submissions made during opposition proceedings, they presented arguments as to why claim 2 of auxiliary requests VIII and IX met the requirements of Article 123(3) EPC.

Claim 1 of auxiliary request I reads as follows (emphasis added by the board):

"1. An isolated antibody having a T cell receptor specificity, specifically bindable **with a binding affinity below 10 nanomolar** to a human major histocompatibility complex (MHC) class I being complexed with a HLA-restricted antigen.

Claim 1 of auxiliary request II reads as follows (emphasis added by the board):

"1. An isolated recombinant antibody with antigen-specific and MHC-restricted specificity of T cells directed towards human T-cell epitopes, said antibody being specifically bindable **with a binding affinity below 10 nanomolar** to a human major histocompatibility complex (MHC) class I being complexed with a HLA-restricted antigen."

Claim 1 of auxiliary request III reads as follows (emphasis added by the board):

"1. An isolated recombinant antibody with antigen-specific and MHC-restricted specificity of T cells directed towards human cancer T-cell epitopes, said antibody being specifically bindable **with a binding affinity below 10 nanomolar** to a human major histocompatibility complex (MHC) class I being complexed with a HLA-restricted antigen."

Claim 1 of auxiliary request IV reads as follows (emphasis added by the board):

"1. An isolated antibody specifically bindable with **a binding affinity below 10 nanomolar** to a human major histocompatibility complex (MHC) class I being complexed with a HLA-restricted antigen, said binding affinity being measured in a competition binding assay as described in the MATERIALS AND EXPERIMENTAL METHODS section of the description, wherein said antibody does not bind said human MHC class I in the absence of said HLA-restricted antigen, wherein said antibody does not bind said HLA-restricted antigen in the absence of said human MHC class I."

Claim 1 of auxiliary request V reads as follows (emphasis added by the board):

"1. An isolated antibody specifically bindable with **a binding affinity below 10 nanomolar** to a human major histocompatibility complex (MHC) class I being complexed with a HLA-restricted antigen, wherein said antibody does not bind said human MHC class I in the absence of said HLA-restricted antigen, wherein said antibody does not bind said HLA-restricted antigen in the absence of said human MHC class I; wherein said MHC class I molecule is HLA-A2."

Claim 1 of auxiliary request VI reads as follows (emphasis added by the board):

"1. An isolated antibody having a T cell receptor specificity, specifically bindable **with a binding affinity below 10 nanomolar** to a human major histocompatibility complex (MHC) class I being

complexed with a HLA-restricted antigen,; wherein said MHC class I molecule is HLA-A2."

Claim 1 of auxiliary request VII reads as follows (emphasis added by the board):

"1. An isolated recombinant antibody with antigen-specific and MHC-restricted specificity of T cells directed towards human T-cell epitopes, said antibody being specifically bindable **with a binding affinity below 10 nanomolar** to a human major histocompatibility complex (MHC) class I being complexed with a HLA-restricted antigen,; wherein said MHC class I molecule is HLA-A2."

Claims 1 and 2 of auxiliary request VIII read as follows:

"1. A method of producing an antibody comprising:
immunizing a genetically engineered non-human mammal having cells expressing said human major histocompatibility complex (MHC) class I with a complex of a single-chain MHC class I and said HLA-restricted antigen, said single-chain MHC class I including a functional human β-2 microglobulin amino acid sequence directly or indirectly covalently linked to a functional human MHC class I heavy chain amino acid sequence being bacterially produced in *E. coli* inclusion bodies;
isolating mRNA molecules from antibody producing cells of said non-human mammal;
producing a phage display library displaying protein molecules encoded by said mRNA molecules; and
isolating at least one phage from said phage display library by selecting against said complex of said single-chain MHC class I and said HLA-restricted

antigen, said at least one phage displaying said antibody specifically bindable with said affinity below 10 nanomolar to said human major histocompatibility complex (MHC) class I being complexed with said HLA-restricted antigen.

2. An isolated antibody obtainable by the method of claim 1, wherein said antibody does not bind said human MHC class I in the absence of said HLA-restricted antigen, wherein said antibody does not bind said HLA-restricted antigen in the absence of said human MHC class I."

Claim 1 of auxiliary request IX corresponds to claim 1 of auxiliary request VIII while claim 2 reads as follows:

"2. An isolated antibody obtainable by the method of claim 1, wherein said antibody has T cell receptor specificity."

IX. In response, appellant II presented arguments as to why the subject-matter of claim 1 of auxiliary requests IV to VIII contained added subject-matter and as to why claim 2 of auxiliary request IX failed to meet the requirements of Article 123(3) EPC.

X. The board summoned the parties to oral proceedings, as requested by the parties, and sent a communication pursuant to Article 15(1) RPBA setting out its preliminary opinion on the case.

XI. By letter dated 17 January 2019, appellant I withdrew its appeal.

XII. At the oral proceedings before the board, nobody attended on behalf of the respondent and the party as of right, as communicated to the board in advance in writing. Appellant II ("appellant") attended. At the end of the oral proceedings the Chair announced the board's decision.

XIII. The appellant's arguments, submitted in writing and during the oral proceedings, in so far as they are relevant for the present decision, can be summarised as follows:

Main request (claims as granted)

Added subject-matter (Article 100(c) EPC) - claim 1

Page 4, lines 3 to 5 of document D24 provided no basis for the feature in claim 1 "*binding affinity below 10 nanomolar*". This passage described an "*isolated molecule comprising an antibody specifically bindable with a binding affinity below 20 nanomolar, preferably below 10 nanomolar*", but not an isolated antibody having an affinity below 10 nanomolar.

The fact that a molecule comprising the antibody had a certain affinity did not mean that a molecule consisting (solely) of the antibody necessarily had the same affinity. Therefore, in the present case the term "comprising" did not provide a basis for "consisting".

The only other mention of an affinity "*below 10 nanomolar*" was on page 15 of document D24 in the context of "*a method of producing an antibody specifically bindable with a binding affinity below 20 nanomolar*", see document D24, page 14, line 22. This method involved a step of *isolating* a "*phage displaying*

the antibody specifically bindable with the affinity below 10 nanomolar". Thus, the product of the method step was a phage displaying an antibody on its surface, instead of an isolated antibody and thus, on page 15, lines 2 to 5, defined the affinity of the phage displaying the antibody rather than the affinity of the antibody per se.

The teaching on pages 14 to 15 was consistent with the disclosure on page 4. The "*isolated molecule comprising an antibody*" was a phage comprising (displaying) the antibody. The phage displaying the antibody had an apparent affinity of 10 nanomolar while the isolated antibody had a binding affinity below 20 nanomolar. A higher apparent binding affinity was typically associated with a phage displaying the antibody relative to the isolated antibody, because the phage presented multiple copies of the antibody, resulting in an avidity effect.

Auxiliary requests I to VII

Added subject-matter (Article 123(2) EPC) - claim 1

The feature relating to the binding affinity "*below 10 nanomolar*" appearing in claim 1 of all of these requests added subject-matter, for the same reasons as those explained in respect of claim 1 of the main request.

Auxiliary requests VIII and IX

Extension of protection (Article 123(3) EPC) - claim 2

Claim 2 of auxiliary request VIII was a new claim, directed to an "*isolated antibody obtainable by the method of claim 1*".

The method of claim 1 of this request comprised several steps, the last step being isolating at least one phage, said phage "*displaying said antibody specifically bindable with said affinity below 10 nanomolar*". This method corresponded to the method disclosed in the passage bridging pages 14 and 15 of document D24. According to page 14, line 22, this method resulted in an antibody which, when detached from the phage, had a binding affinity below 20 nanomolar.

The method according to claim 1 thus had to be understood to result in an antibody with a binding affinity below 20 nanomolar, not below 10 nanomolar.

Hence, the "*obtainable by*" feature of claim 2 imparted to the antibody claimed therein the feature that it had an affinity of below 20 nanomolar.

Claim 2 therefore covered antibodies that were not covered by claim 1 as granted. Hence, claim 2 did not meet the requirements of Article 123(3) EPC.

The same objection applied, *mutatis mutandis*, to claim 2 of auxiliary request IX.

XIV. The respondent's arguments, submitted in writing, in so far as they are relevant for the present decision, can be summarised as follows:

Main request (claims as granted)

Added subject-matter (Article 100(c) EPC) - claim 1

The binding affinity of 10 nanomolar recited in claim 1 found a clear basis at page 4, lines 3 to 7 of the earlier application. There was no intention, in the reference to a "*molecule*" on page 4, to refer to a phage. On reading the next paragraph at page 4, it was clear that the wording "*molecule comprising an antibody*" was used to cover embodiments including the antibody conjugated to identifiable or therapeutic moieties. The identifiable moiety might be a label. The skilled person knew that such labels did not contribute to the affinity of the conjugate to its target. Therefore, the feature "*below 10 nanomolar*" was clearly and unambiguously related to the sole antibody as disclosed implicitly at page 4, lines 3 to 7.

Step (iv) of the method disclosed on page 15 could also be a suitable basis for covering the antibody directly obtainable from the disclosed method.

Auxiliary requests I to VII

Added subject-matter (Article 123(2) EPC) - claim 1

No further arguments as regards the feature "*binding affinity below 10 nanomolar*" were provided.

Auxiliary requests VIII and IX

Extension of protection (Article 123(3) EPC) - claim 2

The antibodies of claim 2 of auxiliary request VIII included all the restrictions applying to the antibodies of claim 1 of the main request and therefore complied with the requirements of Article 123(3) EPC.

Antibodies with T-cell receptor specificity inherently had the binding specificities of the antibodies of claim 1 of the main request. Therefore, claim 2 of auxiliary request IX complied with the requirements of Article 123(3) EPC.

XV. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested in writing that the appeal be dismissed and the patent be maintained as granted or, alternatively, that the patent be maintained in amended form on the basis of the set of claims of one of auxiliary requests I to III filed on 27 December 2013, auxiliary requests IV to VII filed with the reply to the appellants' statements of grounds of appeal, and auxiliary requests VIII to IX corresponding to auxiliary requests IV to V originally filed on 28 November 2014.

Reasons for the Decision

1. The appeal of appellant II complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

Parties to these appeal proceedings

2. After the withdrawal of their opposition, opponent 3 ceased to be a party to the present appeal proceedings. No issues, other than those relating to compliance of the patent with the EPC, had been raised by or against them.

After appellant I's withdrawal of their appeal, they became a party as of right to the present appeal proceedings pursuant to Article 107 EPC.

Appellant II remained the sole appellant.

Absence from the oral proceedings

3. Neither the respondent nor the party as of right attended the oral proceedings, although they were duly summoned. The board decided to continue the proceedings in their absence and treated them as relying on their written case (Rule 115(2) EPC and Article 15(3) RPBA).

Main request (claims as granted)

Added subject-matter (Article 100(c) EPC) - claim 1

4. Claim 1 is directed to an isolated antibody specifically bindable with a binding affinity below 10 nanomolar to a human major histocompatibility complex (MHC) class I being complexed with a HLA-restricted antigen (see section II).

5. The feature "*affinity below 10 nanomolar*" in claim 1 as granted was added during examination proceedings (see decision under appeal, points 22.6.1 and 22.6.2) and thus constitutes an amendment which must not introduce

subject-matter which extends beyond the content of the application as filed (Article 123(2) EPC).

6. In the decision under appeal, reference was made to the earlier application as filed (document D24). It is undisputed that the passages which, in the decision under appeal, were held to provide a basis for the subject-matter of claim 1 (see below, point 7) are identical in the earlier application as filed and the application as filed. In the following, reference is therefore made to the earlier application as filed (document D24).

7. The opposition division decided that page 4, lines 3 to 5, and the passage at page 15, lines 2 to 5, of document D24 disclosed an isolated antibody with a binding affinity below 10 nanomolar (see decision under appeal, point 22.6.4). The appellant disputes this.

8. The passage at page 4, lines 3 to 7, of document D24 reads as follows: "*according to one aspect of the present invention there is provided an isolated molecule comprising an antibody specifically bindable with a binding affinity below 20 nanomolar, preferably below 10 nanomolar, to a human major histocompatibility complex (MHC) class I being complexed with a HLA-restricted antigen.*" [emphasis added]

9. The opposition division held that it was commonly accepted that in the context of a patent application the term "comprising" implicitly encompassed the term "consisting" and that therefore the passage at page 4, lines 3 to 5, of document D24 implicitly also disclosed

an isolated molecule consisting of an antibody having an affinity below 10 nanomolar (see decision under appeal, point 22.6.4).

10. The board does not concur with the opposition division's view. Whether the skilled person would construe the term "comprising" as encompassing "consisting of" depends on the circumstances of the individual case, and, in this regard, on the context in which the term is used. Here, firstly, the disclosure that an isolated molecule comprises an antibody is technically meaningful, although the language may be perceived as somewhat unusual in the technical field of antibodies. Secondly, the expression "*isolated molecule comprising an antibody*" is used throughout document D24, giving the skilled person the impression that there must have been a reason for employing this language instead of specifically referring to "an isolated antibody".

11. The respondent's argument that the term "*molecule*" was not meant to refer to a phage cannot persuade the board to take a different view, since the board's reasoning does not rely on this interpretation of the term "*molecule*".

12. Thus, the skilled person would not derive from the passage on page 4 the implicit disclosure of an isolated antibody that necessarily had a binding affinity below 10 nanomolar.

13. The further passage held to provide a basis for the binding affinity feature (see point 7 above) bridges pages 14 and 15 in document D24 and discloses that "[a]*ccording to an aspect of the present invention there is provided a method of producing an antibody*

specifically bindable with a binding affinity below 20 nanomolar to a human major histocompatibility complex (MHC) class I which is complexed with a HLA-restricted antigen" (see page 14, lines 22 to 25). The method comprises four steps and involves immunising a genetically engineered non-human mammal, isolating mRNA molecules from antibody producing cells, producing a phage display library and as step (iv) "*isolating at least one phage from the phage display library, the at least one phage displaying the antibody specifically bindable with the affinity below 10 nanomolar to the human major histocompatibility complex (MHC) class I being complexed with the HLA-restricted antigen*" (see page 15, lines 2 to 6).

14. The opposition division held that the passage at page 15, lines 2 to 5, of document D24 defined the affinity of the antibody and not the affinity of the phage displaying the antibody.

15. The board does not concur with this view either. The passage bridging pages 14 and 15 discloses a method for producing an antibody with a binding affinity of below 20 nanomolar, which method involves a step of isolating a phage displaying the antibody specifically bindable with an affinity below 10 nanomolar. The teaching that an antibody displayed on a phage has a higher affinity than that of the isolated antibody would make sense to the skilled person, who is aware that the binding affinity of an antibody is increased as a consequence of the avidity effect caused by the binding of multiple antibodies to an antigen. In the board's opinion, the skilled person thus has no reason to assume that page 15, lines 2 to 6 defines the affinity of the antibody *per se*.

16. Hence, the skilled person would not derive from this passage the disclosure of an isolated antibody having a binding affinity of below 10 nanomolar, either.

17. Consequently, the board decides that the ground for opposition under Article 100(c) EPC prejudices the maintenance of the patent as granted, at least for the reason that claim 1 relates to subject-matter extending beyond the content of the application as filed.

Auxiliary requests I to VII

Added subject-matter (Article 123(2) EPC) - claim 1

18. Claim 1 of auxiliary requests I to VII comprises the same binding affinity feature - below 10 nanomolar - as claim 1 of the main request (see sections II and VIII). Accordingly, these requests fail to meet the requirements of Article 123(2) EPC for the same reasons as those given above for claim 1 of the main request.

Auxiliary requests VIII and IX

Extension of protection (Article 123(3) EPC) - claim 2

19. Compared to the claims as granted, claim 2 of auxiliary request VIII is new, in that it defines the isolated antibody by reference to a process, as: "*an isolated antibody obtainable by the method of claim 1 and having a certain binding specificity*". Being a product-by-process claim, it confers absolute protection on the antibody, regardless of the process by which it is prepared. The issue to be decided is whether or not claim 2 of auxiliary request VIII covers any antibodies that were not covered by the claims as granted.

20. Claim 1 as granted relates to an isolated antibody specifically bindable with a binding affinity below 10 nanomolar to a human major histocompatibility complex (MHC) class I being complexed with a HLA-restricted antigen (see section II). Of the set of granted claims, this claim gives the broadest scope of protection. Thus, an answer to the question can be given by a comparison with this claim alone.

21. The binding affinity of the antibody obtainable by the method of claim 1 is not explicitly indicated in claim 2 of auxiliary request VIII. In the board's opinion, claim 2 could only be considered to be limited to an isolated antibody specifically bindable with a binding affinity below 10 nanomolar if this binding affinity was the inevitable consequence of the process as defined in claim 1 of this request.

22. This process comprises as the final step the isolation of "*one phage displaying said antibody specifically bindable with said affinity below 10 nanomolar*" to said human major histocompatibility complex (MHC) class I being complexed with said HLA-restricted antigen (see section VIII). However, the corresponding antibody, when isolated from the phage displaying it, has a lower binding affinity (see also point 15 above).

23. Thus, a binding affinity below 10 nanomolar is not the inevitable consequence of the process as defined in claim 1. Consequently, claim 2 of auxiliary request VIII covers antibodies that were not covered by claim 1 as granted.

24. In claim 2 of auxiliary request IX, the isolated antibody is likewise defined by reference to the process of claim 1 - which is the same method as that

of claim 1 of auxiliary request VIII - and further by the feature "*wherein said antibody has T cell receptor specificity*".

25. The latter feature is a definition of the antigen to which the antibody binds. It does not amount to an implicit definition of the affinity of the antibody.

26. Hence, the affinity of the antibody is defined by reference to the method in the same way as in claim 2 of auxiliary request VIII, and consequently the observations above apply *mutatis mutandis*.

27. The respondent's argument in relation to claim 2 of both auxiliary requests VIII and IX, namely that the defined antibodies include all the restrictions applying to the antibodies of claim 1 as granted, thus fails.

28. The board concludes that claim 2 of both auxiliary requests VIII and IX extends the scope of protection conferred by the claims beyond the protection conferred by the claims of the granted patent. The requirements of Article 123(3) EPC are not fulfilled.

Conclusion

29. In the absence of an allowable claim request, the patent is to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

S. Lichtenvort G. Alt

Decision electronically authenticated