BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

D E C I S I O N
of 8 June 2006

Case Number: T 0298/05 - 3.3.08

Application Number: 99914725.9

Publication Number: 1071763

IPC: C12N 15/11

Language of the proceedings: EN

Title of invention:
Vaccine formulations comprising antiidiotypic antibodies which immunologically mimic group B streptococcal carbohydrates

Applicant:
Chiron S.r.l.

Opponent:
-

Headword:
Group B Streptococcus/CHIRON

Relevant legal provisions:
EPC Art. 83, 56

Keyword:
"Main request - sufficency of disclosure - (yes)"
"Inventive step (yes)"

Decisions cited:
G 0002/03

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0298/05 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 8 June 2006

Appellant: Chiron S.r.l
Via Fiorentina, 1
I-53100 Siena (IT)

Representative: Hallybone, Huw George
Carpmaels and Ransford
43 Bloomsbury Square
London WC1A 2RA (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 21 October 2004 refusing European application No. 99914725.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
M. B. Günzel

Summary of Facts and Submissions

I. European patent application No. 99 914 725.9 published as International application No. WO 99/54457 with the title "Vaccine formulations comprising antiidiotypic antibodies which immunologically mimic group B streptococcal carbohydrates" was refused by the examining division. The basis for the refusal was insufficiency of disclosure in relation to the subject-matter of claims 1 to 18 belonging to the claim request filed on 10 December 2003. Claim 1 of this request read as follows:

"1. A single-chain Fv fragment that is capable of eliciting a protective immune response against the capsular polysaccharide of group B *Streptococcus.*"

At an earlier stage during examination (communication of 8 July 2003), an objection for lack of inventive step was also raised by reference to the international preliminary examination report. As also appears in the decision under appeal, this objection was reiterated in the summons to oral proceedings. It is, however, not reasoned in the decision per se.

II. Originally filed claims 1, 5, 6, 8 and 22 read as follows:

"1. A peptide, oligopeptide or polypeptide compound that is capable of eliciting a protective immune response against the capsular polysaccharide of group B *Streptococcus*.

5. The compound according to any preceding claim, which comprises an antibody or antibody fragment.

6. The compound of claim 5 which comprises an scFv fragment.

8. The compound according to any preceding claim wherein the structure of the compound mimics an antigenic determinant of the capsular polysaccharide of group B *Streptococcus.*

22. A method of selection of a compound according to any one of claims 1 to 10 comprising the steps of:

a) immunising a mammal with an antibody against a capsular polysaccharide of group B *Streptococcus*;

b) removing spleen cells from the immunized mammal and selecting for cells that bind to the antibody;

c) separating mRNA species from selected spleen cells and producing a phage library expressing proteins encoded by the mRNA species; and

d) selecting for recombinant phage expressing compounds of interest."

III. The appellant (applicant) filed a notice of appeal against this decision, paid the appeal fee and submitted a statement of grounds of appeal together with a main claim request (claims 1 to 26 filed on 10 December 2003) and an auxiliary claim request (claims corresponding to claims 19 to 26 of the same

request). The appellant also requested a refund of the appeal fee.

IV. The appealed decision was not rectified by the examining division and the case was remitted to the board of appeal (Article 109(2) EPC).

V. The board sent a communication pursuant to Article 110(2) EPC raising a number of objections under Article 123(2), 84 and 53a EPC against claims 1, 19 and 25 of the main request.

VI. On 19 January 2006, the appellant filed a further submission in answer to this communication together with a new main request.

VII. The board sent another communication pursuant to Article 110(2) EPC, with observations on the newly filed main request.

VIII. On 18 April 2006, the appellant answered to this communication and filed a new main request and five auxiliary requests in replacement of the previous requests. The new main request comprised 24 claims, claims 1 and 18 read as follows:

"1. A single-chain Fv fragment that is capable of eliciting a protective immune response against the capsular polysaccharide of group B *Streptococcus*, wherein the structure of the single-chain Fv fragment mimics an antigenic determinant of a capsular polysaccharide of group B *Streptococcus.*

18. A method of selection of a single-chain Fv fragment that is capable of eliciting a protective immune response against the capsular polysaccharide of group B *Streptococcus* comprising the steps of:

a) immunising a mammal with an antibody against a capsular polysaccharide of group B *Streptococcus*, wherein the mammal is not a human;

b) removing spleen cells from the immunized mammal and selecting for cells that bind to the antibody;

c) separating mRNA species from selected spleen cells and using the separated mRNA as a template for reverse transcriptase to produce cDNA;

d) using the cDNA produced in step c) to construct a recombinant phage library expressing single-chain Fv fragments; and

e) selecting for recombinant phage expressing single-chain Fv fragments of interest."

Dependent claims 2 to 6 related to further features of the single-chain Fv fragment (scFv) of claim 1. Claim 7 to 11 were directed to pharmaceutical compositions comprising the scFv fragment according to any preceding claims. Claims 12 to 16 were formulated as first or second medical use claims of the scFv fragment. Claim 17 related a vaccine comprising it. Claims 19 to 23 were respectively directed to nucleic acid molecules, vectors and recombinant hosts encoding/carrying/transformed by the scFv fragment/

DNA. Claim 24 related to a recombinant method of preparing scFv according to any one of claims 1 to 6.

IX. On 16 May 2006, the rapporteur inquired from the appellant by telephone whether or not the request for refund of the appeal fee filed with grounds of appeal was maintained. On the same day, the appellant informed the board by fax letter that this request was withdrawn.

X. On 22 May 2006, the registrar of the board asked the appellant to provide a clean copy of the main request filed on 18 April 2006. A clean copy of this request was filed on 22 May 2006.

XI. The following documents are mentioned in the present decision:

(1): Pincus, S.H. et al., The Journal of Immunology, Vol. 160, No.1, pages 293 to 298, January 1998;

(3): Bona, C.A., Nature Medicine, Vol.4, No.6, pages 668 to 669, June 1998;

(4): Magliani, W. et al., Nature Biotechnology, Vol.15, pages 155 to 158, February 1997;

(5): Lamarre, A. and Talbot, P., Viral Immunology, Vol.10, No.4, pages 175 to 182, 1997;

(6): Teti, G. et al., Hybridoma, Vol.11, pages 13 to 22, 1992 (cited in the application).

XII. The appellant's arguments insofar as relevant to the present decision may be summarized as follows:

Article 83 EPC; sufficiency of disclosure

– The examining division took the wrong approach when refusing the application for the reason that the exemplified phage expressing a scFv fragment (C10) had not been deposited and, thus, could not be reproduced. Indeed, the question of sufficiency should not be judged on whether or not C10 - which was not claimed - was reproducible but rather on whether the application taught to generally obtain scFv fragments that fell within the scope of the claim.

– The relevant methodology was described in detail at pages 34 to 37 of the application. By using it, the inventors did not only find C10 but also found five other phage clones (page 37, lines 8 and 9).

Producing a library of recombinant phages was a simple technique that could be carried out using off-the-shelf kits known in the art. Screening for the presence of recombinant phages expressing scFv fragments was equally a matter of routine (ELISA tests for binding to known anti-capsular polysaccharide (CPS) monoclonal antibodies). All soluble scFv fragments obtained by this method had shown themselves capable of eliciting a protective immune response and, therefore, the examining division was wrong in alleging that isolating such scFv fragments could not be achieved in a reliable and reproducible manner.

– Sufficiency of disclosure also existed over the scope of the claims. In particular, claim 1 needed not be restricted to scFv fragments capable of eliciting a protective immune response against the type III CPS antigen. The various group B *Streptococcus* serotypes shared the same trisaccharide core, the difference between them arising only from the way in which the core was modified. There was, thus, no logical reason why the scFv fragments would be able to elicit a protective immune response against certain group B streptococci but not against others.

In the same manner, it was not necessarily essential for the antiidiotypic antibody (which the scFv fragments were derived from) to have been raised against anti-CPS antibody which was capable of protective activity against group B *Streptococcus*. If the original anti-CPS antibody was non-protective, the scFv fragments would mimic non-protective CPS epitopes but they may nonetheless be able to provide protection by another mechanism, namely, they may elicit a cell-mediated response against these epitopes, even though the CPS itself would not be able to do so.

For these reasons, the requirements of Article 83 EPC were fulfilled.

Article 56 EPC; inventive step; claim 1

Document (1) taught that 9mer and 12mer peptides having aromatic, acidic and hydrophobic residues could be used

to mimic the group B *Streptococcus* capsular polysaccharide antigen. It did not indicate that immune memory or passive immunity could be obtained by using these peptides. In contrast, the inventors found that scFv could be used to elicit immune memory and passive immunity. In doing so, they made a significant contribution to the art. Due to the structural differences existing between the scFv fragments and the prior art peptides, there would be no reason to expect that the scFv fragments would act in the same way as the prior art peptides, nor, a fortiori, to expect that they would provide an improvement on said peptides.

The significance of the inventors' findings was acknowledged in document (3), a review by an independent person which confirmed that the invention represented a non-obvious and advantageous improvement.

XIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed on 22 May 2006 (clean copy of the main request filed on 18 April 2006), alternatively on the basis of either one of the auxiliary requests 1 to 5 also filed on 18 April 2006.

Reasons for the decision

Main request (claims 1 to 24) filed on 22 May 2006
Articles 123(2) and 84 EPC

1. The subject-matter of claim 1 finds a basis in claim 8 of the application as filed (depending on claim 6 itself depending on claim 1).

The subject-matter of claim 18 finds a basis in claim 22 of the application as filed (with back-reference to claim 8), page 7, 35 and 36. Claim 18 also contains the hitherto undisclosed disclaimer "wherein the mammal is not a human". In accordance with the decision of the Enlarged Board of Appeal G 2/03 (OJ EPO 2004, 448, point 2.4 of the reasons), this disclaimer which was introduced to satisfy the requirements of Article 53a EPC does not constitute added subject-matter.

Claims 2 to 6 respectively correspond to originally filed claims 2 to 4, 9 and 10. Claims 7 to 17 correspond to originally filed claims 11 to 21. Claims 19 to 24 correspond to originally filed claims 24 to 28 and 30.

2. Furthermore, in the board's judgment, the claimed subject-matter is clear and supported by the description.

3. The requirements of Articles 123(2) and 84 EPC are fulfilled.

Articles 54 and 57 EPC; novelty and industrial applicability

4. There are two prior art documents on file which describe scFv fragments, namely documents (4) and (5), but these scFv fragments originate from anti-idiotypic antibodies of a yeast killer toxin or of coronaviruses; they are not scFv fragments capable of eliciting a protective immune response against the capsular polysaccharide (CPS) of group B *Streptococcus*. Novelty is acknowledged.

5. Industrial applicability of the scFv fragments is to be seen in their protective effect against group B *Streptococcus* infection and, thus, in their use in the medical field.

6. The requirements of Articles 54 and 57 EPC are fulfilled.

Article 83 EPC; sufficiency of disclosure

7. On page 33 of the application as filed, numerous references are made to documents representing the common general knowledge pertinent for putting the method of claim 18 into practice, this being the method by which a single-chain Fv fragment as claimed in claim 1 is obtained.

8. The protocol for obtaining scFv fragments which is described in detail from page 34 to page 37 only involves conventional techniques of molecular biology. Worthy of attention is the fact that a specific monoclonal antibody (mAb) is used to carry out the first step in the method of claim 18, namely P9D8. On page 35, lines 1 and 2, P9D8 is described by reference to Teti et al., 1992 (introduced in these proceedings as document (6)). This document discloses the production of 41 mAbs directed against type III group B *Streptococcus* (summary) as well as the way to determine their protective capacity (page 16). It, thus, provides evidence that the skilled person would have no problems in isolating anti-CPS mAbs - irrespective of whether they are protective or not. Consequently, P9D8 is not

considered essential for putting the claimed method into practice.

9. How to test the scFv fragments of claim 1 for their protective capacity is described in detail from page 38 to page 44 of the application.

10. In the course of appeal proceedings, the board made the observation that claim 1 encompassed scFv fragments capable of eliciting a protective immune response against the CPS of group B *Streptococci* irrespective of their serotypes, whereas the method described in the application was carried out in relation to group B *Streptococcus* with a type III CPS. It was also pointed out that the method of claim 18 comprised the use of an original anti-CPS mAb (step a)) which, in contrast to P9D8, would not be protective. The appellant answered that the various serotypes of group B *Streptococcus* were structurally "alike" and, thus, the claimed method would be fully expected to work for all serotypes. Furthermore, in its view, there was no necessity for the original anti-CPS antibody to be protective in order to obtain scFv fragments capable of eliciting a protective immune response as end products of the claimed method (see Section VIII, supra). In the absence of any evidence to the contrary, the board accepts that the subject-matter of claim 18 is reproducible over the scope of the claim and, consequently, also accepts sufficiency of disclosure in relation to the claimed subject-matter as a whole.

11. For the reasons given in points 7 to 10 supra, the requirements of Article 83 EPC are fulfilled.

Article 56 EPC; inventive step

12. As already mentioned above (Section I, supra), the decision under appeal indicates that an objection was raised under Article 56 EPC in the summons to oral proceedings by the examining division. However, no reasoning was presented in respect of this issue in the decision under appeal. For sake of procedural expediency, the board will now deal with it rather than send the case back to the first instance.

13. The closest prior art is document (1) which relates to peptides that mimic the group B *Streptococcal* type III capsular polysaccharide antigen. In the introductory part of the document, it is explained that the carbohydrates of group B *Streptococcus* are notably poor immunogens, which makes it difficult to protect neonates from infection. The work described is identified as an attempt to enhance immunogenicity and the method which is proposed - using peptides which mimic the structure of the polysaccharide as immunogens - is said to be an alternative to that already described in the art - conjugating the polysaccharide to protein carriers. Thus, a phage display library that expresses peptides with random amino acid sequences is tested for its ability to bind a monoclonal antibody, namely mAbS9 which is protective against the polysaccharide and two recombinant phages are identified which specifically bind to this antibody. The peptides which they display are identified by their amino acid sequence. Once isolated, they are used to immunize mice. All mice produce a significant antibody response and the antibodies recognize the purified type III capsular polysaccharide as well as the

corresponding group B *Streptococcus.* The authors, thus, conclude to the antigenicity and immunogenicity of the peptide mimetics. Furthermore, it is suggested that "*The incorporation of such peptides into vaccine preparations may enhance the efficacy of vaccines in inducing Ab responses to important carbohydrate epitopes.*" (summary). In the board's view, this sentence may be taken as an indication that the ultimate aim of the research would be to obtain peptide mimetics capable of eliciting protective immunity. No evidence is, however, produced that the specific peptide mimetics described in document (1) have such a capacity.

14. On page 297 of the same document (right-hand column), the reader is also reminded that anti-idiotypic antibodies had been shown in the prior art to be able to elicit an immune response to carbohydrate antigens of *Streptococcus pneumoniae, Pseudomonas aeruginosa and E.coli,* and that one example existed of a synthetic peptide mimetic capable of eliciting protective immunity, namely the peptide mimetic of the capsular polyssacharide antigen of the meningococcal group C. The sequence of this peptide had been devised on the basis of a sequence analysis of an anti-idiotype antibody which mimicked the meningococcal polysaccharide antigen.

15. Starting from the closest prior art, the problem to be solved may be defined as providing mimetic compounds capable of eliciting a protective immune response against the capsular polysaccharide antigen of group B *Streptococcus*.

16. The provided solution is a very specific group of oligopeptides, namely **scFv fragments** with a structure mimicking an antigenic determinant of a capsular polysaccharide.

17. In the board's judgment, in view of the suggestion in document (1) that random peptide mimetics may enhance vaccine efficiency, the obvious course of action for obtaining mimetic compounds capable of eliciting a protective immune response would be to look for further random peptide mimetics and assess their capacity of eliciting such a response. The proposed solution is significantly different insofar as the claimed "peptides" are not random but rather belong to a very specific group: that of scFv fragment mimetics. There is no suggestion at all in document (1) that such kind of molecules might be efficacious for fighting streptococcal infections.

18. In this context, it must be emphasized that, although devised on the basis of an anti-idiotypic antibody sequence, the peptide mimetic of the CPS of meningococcal group C mentioned in document (1) (point 14, supra) is not an scFv fragment. As for the capacity of anti-idiotypic antibodies per se of eliciting an immune response against carbohydrate antigens also mentioned in document (1), it does not necessarily imply that a linear molecule such as the single-chain Fv fragment could lead to protective immunity.

19. Thus, in the board's judgment, document (1) on its own is not detrimental to inventive step.

20. There are two prior art documents on file which disclose anti-idiotypic scFv fragments as potential tools against infectious agents (the antigens being proteins rather than carbohydrates). Document (4) describes the production of scFv anti-idiotypic antibodies of a killer toxin from the yeast *Pichia anomala* which are said to have candidacidal activity on *Candida albicans*. On page 157, left-hand column, it is explained that they may act therapeutically like an antibiotic. In the board's judgment, the mechanisms of action of antibiotics and immunogens are so different that the skilled person would not think of combining this teaching with that of document (1) to arrive in an obvious manner to the claimed invention. Document (5) teaches the production of anti-idiotypic scFv fragments to elicit an immune response against coronaviruses but in the abstract, it is explicitly stated that "*These results demonstrate that anti-Ids can be isolated from a phage display library, although high-affinity antigen mimicking phages with antiviral* ***protective*** *capacities were apparently* ***not represented*** *in this library.*" (emphasis added by the board). If anything, this teaching would discourage the skilled person starting from document (1) from looking for scFvs capable of eliciting a protective immune response against the capsular polysaccharide of group B *Streptococcus*.

21. On the contrary, document (3) published between the priority and the filing date of the application (to be taken as an expert document) acknowledges the significance of the findings of the present invention.

22. Inventive step is acknowledged.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order of granting a patent on the basis of:

   - claims 1 to 24 of the main request filed on 22 May 2006, and

   - a description to be adapted thereto, and

   - Figures 1 and 2 as originally filed.

The Registrar: The Chairman:

A. Wolinski L. Galligani