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D E C I S I O N
of 21 January 2005

Case Number: T 0734/00 - 3.3.4

Application Number: 95203128.4

Publication Number: 0711563

IPC: A61K 39/02

Language of the proceedings: EN

Title of invention:
Novel Borrelia vaccine

Applicant:
SYMBICOM AB

Opponent:
-

Headword:
Novel Borrelia vaccine/SYMBICOM AB

Relevant legal provisions:
EPC Art. 83, 54, 56
EPC R. 28

Keyword:
"New main requests: Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0734/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 21 January 2005

Appellant: SYMBICOM AB
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 15 February 2000 refusing European application No. 95203128.4 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
R. Moufang

Summary of Facts and Submissions

I. European patent application No. 95 203 128.4 published as EP-A-0 711 563 with the title "Novel Borrelia vaccine" was refused by the examining division for lack of inventive step (Article 56 EPC) of the claims of the main request and of auxiliary requests 1 to 3 then on file.

II. The appellant (applicant) lodged an appeal against this decision.

III. The following documents are cited in the present decision:

(D1) Howe T.R. et al., Infection and Immunity, Vol. 54, No. 1, pages 207-212 (October 1986);

(D2) Coleman J.L. et al., The Journal of Infectious Diseases, Vol. 155, No. 4, pages 756-765 (April 1987);

(D6) Benach J.L. et al., Annals of the New York Academy of Sciences, Vol. 539, pages 115-125 (1988);

(D8) Howe T.R. et al., Science, Vol. 227, pages 645-646(8 February 1985);

(D28) Declaration by Drs. Howe, Bergström and Barbour dated 5 January 2005, 7 January 2005 and 5 January 2005, respectively;

(D29) Declaration by Drs. Bergström and Barbour dated 6 March 1997 and 26 February 1997, respectively;

(D30) Letter from the American Type Culture Collection dated 12 February 1985.

IV. A communication was sent, expressing inter alia the board's provisional view on the novelty and inventive step of the claims on file in view of document (D1). In response thereto the appellant provided inter alia Declaration (D28).

V. Oral proceedings were held on 21 January 2005, during which the appellant submitted a New Main Request, of which claim 1 read as follows:

"1. A substantially pure entire OspA protein free from other B. burgdorferi spirochaete related material."

Claims 2 to 6 related to specific embodiments of the protein of claim 1, whereas claims 7 to 17 covered compositions comprising an immunologically effective amount of the substantially pure protein.

VI. The appellant's arguments were essentially as follows:

Article 83 and Rule 28 EPC

- The Borrelia burgdorferi strain ATCC 35210 (see claims 2 and 16) was available to the public.

Novelty

- Before the priority date of the present application no amino acid sequence information could be derived from OspA from natural sources because the purified preparations of the prior art lacked homogeneity and moreover the skilled person was not aware of the fact that the N-terminus of the native OspA molecule was blocked by a N-lipidyl moiety.

- Therefore, the only possible route to the claimed substantially pure entire OspA protein, free from other B. burgdorferi spirochaete related material was the recombinant approach disclosed in the present application.

- Documents (D1) and (D8) were non enabling disclosures because the recombinant plasmids pTRH32, pTRH43 and pTRH44 expressing the OspA protein were not available to the public. Plasmid pTRH32 from which plasmid pTRH44 originated was moreover unstable.

Inventive step

- Document (Dl) represented the closest prior art. Plasmid pTRH44 referred to in this document, from which the DNA encoding OspA could be isolated and sequenced, was not available to the public.

- It was a hard task for the skilled person to enter the recombinant route without any available plasmid. Arriving at plasmid pTRH44 was a highly random event involving random transposon Tn5 mutagenesis.

- Therefore, it was not straightforward for the skilled person to repeat the whole work leading to the cloning and sequencing of the OspA gene.

- There was no easier way to the DNA/amino acid sequence of OspA protein, e.g. by sequencing the native protein because the native OspA preparation comprised a great many proteins in the same molecular weight range. Moreover the skilled person was not aware of the fact that the native OspA was N-terminally blocked by a N-lipidyl moiety. Difficulties thus arose in both further purifying the prior art OspA preparations and determining the N-terminal amino acid sequence by standard methods.

- The pTRH44's restriction map disclosed by document (D1) (see Fig. 2) did not enable DNA sequencing. The "EP" fragment was actually only 10 bp long and not 100 bp as indicated in this document. The finding of a ScaI site was a breakthrough for the successful sequencing. Furthermore, the high A-T content rendered sequencing of plasmid pTRH44 difficult.

VII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the new main request consisting of claims 1 to 17 filed at the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

Article 83 and Rule 28 EPC

2. Claims 2 and 16 refer to Borrelia burgdorferi strain ATCC 35210. No objections under Article 83 EPC arise, as the deposited strain was available to the public (see document (D30)).

Novelty (Article 54 EPC)
Documents (D2) and (D6)

3. According to document (D2) (see page 760, lines 19-23), OspA and OspB are eluted from the SDS-PAGE gel in the same fraction, owing to their close proximity to one another (see also Fig. 2 showing the overlap of the 31/34-kDa bands). This fraction is indeed designated as the "31/34-kDa complex" or the "31/34-kDa polypeptides" (see e.g. the legend to Fig. 6). Hence, this unresolved fraction including OspB does not fall under the terms of claim 1, directed to "a substantially pure entire OspA protein free from other B. burgdorferi spirochaete related material."

4. As for document (D6), the authors thereof use the same elution method as in document (D2) yielding the same unresolved "31/34 kDa complex" described in document (D2). This can be derived from page 116, 3rd paragraph of document (D6), stating that "The elution procedures for Osp-A (~31 kDa) and for flagellins (~41 kDa) have been described[2]", reference "2" being document (D2) (see

section III supra). In fact, in the text that follows, "Osp-A (~31 kDa)" is also designated as "eluted Osp-A" (see e.g. page 124, Summary).

5. Document (D6) (see page 116, end of 3rd paragraph) further states that "Only fractions that yielded single bands on silver stained gels were used in these experiments[11]". However, silver staining merely increases sensitivity, i.e. the detection level (visibility) of the bands (see the title of reference 11: "A **sensitive** silver **stain** for detecting..."; emphasis by the board), not the bands' resolution. In conclusion, document (D6) does not disclose any further purification step(s) which would provide OspA in purer form. Hence, the (still) unresolved fraction termed "Osp-A (~31 kDa)" or "eluted Osp-A" in document (D6) is not novelty-destroying for present claim 1.

Documents (D1) and (D8)

6. None of these references enables the provision of OspA free from other B. burgdorferi spirochaete related material (see points 11 to 18 infra).

Conclusions

7. There is no disclosure in the prior art of a substantially pure entire OspA protein free from other B. burgdorferi spirochaete related material. Claim 1 of the main request thus satisfies the requirements of Article 54 EPC. This conclusion also applies to claims 2 to 6, relating to specific embodiments of the protein of claim 1, and to claims 7 to 17, covering compositions comprising the protein of claim 1.

Inventive step (Article 56 EPC)

8. What is claimed is pure OspA, i.e. OspA without any contamination from other B. burgdorferi antigens, to be used e.g. as immunogen. At the priority date of the present application, the claimed subject-matter could theoretically be arrived at by (i) purification of B. burgdorferi preparations, (ii) picking up the gene by means of a DNA probe designed in the light of a partial amino acid sequence of OspA or (iii) isolating the OspA gene and making the recombinant/synthetic protein by conventional techniques in the light of the DNA sequence of the OspA gene and/or the encoded amino acid sequence.

Closest prior art

9. However, as regards route (i) above, nobody succeeded in obtaining the OspA protein in a pure form by using conventional purification methods (see points 3 to 5 supra). As regards further purifying these prior art OspA preparations, the board agrees to the appellant's argument that the skilled was confronted with difficulties arising, inter alia, from the fact (unknown to him/her) that OspA was N-terminal-lipidylated. The board thus concludes that it was not obvious at the priority date of the application in suit to produce pure OspA protein from the native source.

10. As for route (ii) above to the DNA of the OspA gene by picking up the gene by means of a DNA probe designed in the light of a partial amino acid sequence of OspA, there is no evidence before the board that the skilled person could obtain partial (let alone complete) amino

acid sequence information from the native OspA protein described in documents (D2) and (D6). This is because upon cleavage of an OspA protein fraction according to these documents, the result would have been a number of protein fragments derived from OspA and OspB, not necessarily bearing the epitope recognised by e.g. monoclonal antibody H5332. It is thus plausible that the use of one of these fragments for the design of a DNA probe was prevented by the lack of the information that it was actually an OspA fragment.

11. As for the only route (iii) above still open, document (D8) reports the isolation of plasmid pTRH32 carrying a 6 kb DNA fragment from B. burgdorferi. This DNA fragment is shown to encode and to express polypeptides reacting with monoclonal antibodies known to bind to OspA and OspB.

Document (D1) deals with the further restriction enzyme analysis and transposon mutagenesis of the 6 kb DNA fragment of document (D8), which results in the identification of plasmids pTRH43 and pTRH44, the latter carrying a DNA fragment encoding and expressing a polypeptide of the size of OspA (31 kD). Neither document (D8) nor document (D1), however, provide any sequence data for the OspA protein or for the OspA gene.

12. The board views the document (D1) as the closest prior art, since it is concerned with the cloning of the OspA gene devoid of any DNA stretch encoding OspB.

Problem to be solved

13. Departing from document (D1) as the closest prior art, the problem to be solved lies with determining the DNA sequence of the OspA gene and hence the amino acid sequence of the OspA protein encoded by this gene. This key information, in the board opinion, renders possible route (iii) (see point 8 supra), namely the recombinant and/or synthetic production of the protein by conventional techniques. The solution proposed is the DNA/amino acid sequences shown in Figure 5 of the application (see also page 22, lines 41-ff).

14. The question thus arises whether or not the proposed solution, i.e. the elucidation of the DNA sequence encoding the OspA protein and the encoded amino acid sequence, follows from the prior art in an obvious manner.

15. Since plasmid pTRH44 referred to in document (D1) carries a DNA fragment encoding the OspA protein, the possession of this plasmid would have been a decisive tool in the hands of the skilled person wishing to obtain the necessary DNA/amino acid sequences from the OspA gene, a key information to the recombinant and/or synthetic production of the OspA protein by conventional techniques.

16. As for the possibility that the skilled person could arrive at plasmid pTRH44 on the basis of the information provided by documents (D1)/(D8), it should be noted that this plasmid results from further work (restriction enzyme analysis and transposon mutagenesis) performed on plasmid pTRH32 bearing a 6 kb DNA fragment

from B. burgdorferi (see document (D8)). This unstable and not viable plasmid pTRH32 (see document (D29), paragraph 6) had already been obtained by chance (one out of 10,000 colonies: see document (D8), page 645, end of r-h column). Transposon mutagenesis performed on this plasmid that led to the identification of plasmid pTRH44 was a no less random technique. Therefore, the board concludes that it was an unreliable chance event that the skilled person could arrive at plasmid pTRH44 on the basis of the information provided by documents (D1) and (D8) alone.

17. As regards the plasmids' public availability, the appellant submitted at the oral proceedings Declaration (D29) to the effect that none of plasmids pTRH32, pTRH43 and pTRH44 referred to in document (D1) was available to the public before the priority date of the present application. From this declaration it appears that the above three plasmids were never distributed to others than the inventors unless it was agreed with the recipient that the plasmids would not be distributed to others (see paragraphs 6 and 19-24 of the Declaration). The board is thus satisfied that before the priority date of the present application, the plasmids disclosed in document (Dl) were not available to the public, so that the skilled person could not have used this means to arrive in an obvious manner at the claimed subject-matter.

18. Therefore, it must be concluded that the DNA and amino acid sequences of the OspA gene, and hence the provision of the OspA protein free from other B. burgdorferi spirochaete related material according to present claim 1, do not follow in an obvious manner

from the prior art. This conclusion also applies to claims 2 to 17, all relying on the protein of claim 1.

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 to grant a patent on the basis of claims 1 to 17 of the new main request filed at oral proceedings and a description to be adapted thereto.

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey