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Datasheet for the decision of 28 June 2018

Case Number: T 1840/15 - 3.3.04

Application Number: 10181233.7

Publication Number: 2353608

IPC: A61K39/095, C07K14/22, A61P31/04

Language of the proceedings: EN

Title of invention:
Polypeptide-vaccines for broad protection against hypervirulent meningococcal lineages

Applicant:
Novartis Vaccines and Diagnostics S.r.l.

Headword:
Trimeric NadA/NOVARTIS

Relevant legal provisions:
EPC Art. 56, 76(1), 111(1)

Keyword:
Main request - subject-matter extends beyond the content of the earlier application (yes)
Auxiliary request 1 - non-obvious alternative
Remittal to the examining division (yes)

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It can be changed at any time and without notice.

Decisions cited:

Catchword:

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Case Number: T 1840/15 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 28 June 2018

Appellant: (Applicant)	Novartis Vaccines and Diagnostics S.r.l. Via Fiorentina 1 53100 Siena (SI) (IT)
Representative:	Marshall, Cameron John Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 12 March 2015 refusing European patent application No. 10181233.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chair	G. Alt
Members:	R. Morawetz
	P. de Heij

Summary of Facts and Submissions

I. The appeal of the applicant (hereinafter "appellant") lies against the decision of the examining division refusing European patent application No. 10 181 233.7, entitled "*Polypeptide-vaccines for broad protection against hypervirulent meningococcal lineages*".

II. The present application is a divisional application of the earlier European patent application No. 03 758 486.9, which has been published as international application WO 2004/032958 (hereinafter "earlier application"), and claims priority from three national applications, GB 0 223 741.0 filed on 11 October 2002, GB 0 305 831.0 filed on 13 March 2003 and GB 0 309 115.4 filed on 22 April 2003.

III. The following documents are referred to in this decision:

D2 WO 01/64922 (7 September 2001)

D5 WO 03/010194 (6 February 2003)

IV. In the decision under appeal the examining division held that the subject-matter of claim 1 of the main request before it lacked inventive step in view of the combined teaching of documents D2 and D5.

It considered that document D2 disclosed a secreted form of NadA which was bactericidal but that document D2 did not disclose a secreted, trimeric form of NadA. However, document D5 was held to disclose that NadA can form oligomers, e.g. dimers, trimers, tetramers or higher. Therefore the skilled person would expect the secreted form of the NadA protein in

document D2 to occur in monomeric and different oligomeric forms.

The claimed trimeric form of NadA was considered to be randomly selected from all the possible oligomers present in the supernatant as disclosed in document D2 (see decision under appeal, page 2, last paragraph to page 5, third paragraph).

Also the subject-matter of claims 1 and 2 of the auxiliary request before the examining division was considered to fail the requirements of Article 56 EPC because it related to a "*process for purifying the non-inventive trimeric NadA by using standard methods*" (*ibid.*, page 5, fourth paragraph to page 6, third paragraph).

V. With the statement of grounds of appeal, the appellant filed a main request and an auxiliary request, both corresponding to the claim requests underlying the decision under appeal.

Claim 8 of the main request reads as follows:

"1. A process for purifying meningococcal NadA in trimeric form from a culture supernatant, wherein the NadA consists of the amino acid sequence of SEQ ID NO: 2, comprising steps of: concentration and diafiltration against a buffer by ultrafiltration; anionic column chromatography; hydrophobic column chromatography; hydroxylapatite ceramic column chromatography; diafiltration against a buffer; and filter sterilisation."

Claim 9 depends on claim 8 and specifies that NadA is expressed from a plasmid encoding SEQ ID NO:1.

VI. The appellant was summoned to oral proceedings and was subsequently informed of the board's preliminary opinion in a communication under Article 15(1) RPBA. The board raised *inter alia* an objection under Article 76 EPC against the subject-matter of claims 8 and 9 of the main request, observing that the process disclosed in the earlier application for purifying meningococcal NadA in trimeric form seemed to include mandatorily a step of gel filtration which was however absent from the process defined in claims 8 and 9 (see points 17 to 19 of the communication).

VII. In reply, the appellant withdrew its request for oral proceedings, filed an auxiliary request 1 and renumbered the previously pending auxiliary request as auxiliary request 2. The board was informed that nobody would be attending the oral proceedings on behalf of the appellant.

Claim 1 of auxiliary request 1 reads as follows:

"1. Recombinant *N. meningitidis* NadA in trimeric form, wherein the NadA consists of the amino acid sequence of SEQ ID NO: 2."

Claim 2 is directed to a composition comprising five different meningococcal antigens. Claims 3 to 7 depend on claim 2 and relate to various embodiments of the composition of claim 2.

VIII. At the end of the oral proceedings, which took place in the appellant's absence, the chair of the board announced the board's decision.

IX. The appellant's arguments as far as relevant to the present decision can be summarised as follows.

Main request

Article 76 EPC - process claims 8 and 9

The process disclosed in the earlier application led to the production of trimeric NadA. The gel filtration analysis merely separated the trimeric form from its aggregates and degradation products, but was not a required step for preparing NadA in trimeric form.

Auxiliary request 1

Admissibility

The objection against the process claims of the main request under Article 76 EPC did not feature in the decision under appeal but was newly raised by the board in its communication. In this claim request the objected process claims 8 and 9 of the main request were deleted. The request should be admitted in the interest of procedural economy.

Article 56 EPC - claim 1

Closest prior art

Document D2 was the closest prior art. It was specifically concerned with the provision of improved approaches for the expression of *Neisserial* proteins (see page 1, lines 12 to 13), as was the present application. Document D2 disclosed that a protein corresponding to the full-length form of the NadA protein of the application (termed 961-L in

document D2) was predominantly monomeric after production in an IPTG-induced culture while it was predominantly oligomeric after production in an over-night uninduced culture (see page 62, lines 14 to 15). Thus, the skilled person would understand from document D2 that IPTG induction disrupted the formation of 961-L (NadA) oligomers.

There was no evidence for the inherent presence of secreted NadA trimers in the supernatant of the culture disclosed in document D2.

Technical problem and its solution

The NadA consisting of SEQ ID NO:2, *i.e.* a truncated form of NadA protein lacking the C-terminal membrane anchor domain, was, when expressed in culture in *E. coli*, a secreted protein that was found in the culture supernatant. A difference between the corresponding protein disclosed in document D2 (termed 961c-L) and the subject-matter of claim 1 was that the NadA was in the form of a trimer.

The technical effect of this difference was a bactericidal NadA which could be easily purified.

The objective technical problem solved was therefore the provision of bactericidal NadA in a form which could be easily purified. The application provided evidence that this technical problem was solved, with the bactericidal activity of the trimeric protein confirmed in the first table on page 34, row (3). The skilled person knew that a secreted protein was more

easily purified than a membrane-bound protein as it did not require cell lysis and extraction from the membrane.

Obviousness

Document D2 taught that disruption of the membrane anchor domain of 961-L prevented the formation of oligomers (see page 62, lines 16 to 17) leading the skilled person to understand that any form of NadA lacking its membrane anchor domain would not form oligomers.

Document D5 only disclosed surface-exposed, membrane-bound oligomers of NadA, which by definition require a membrane anchor domain (see page 26, lines 30 to 33).

In view of the lack of any suggestions in the prior art that secreted NadA consisting of SEQ ID NO:2 could form trimers in the absence of a membrane anchor domain, the skilled person would not have arrived at the solution of a trimeric NadA as claimed.

X. The appellant requested that the decision under appeal be set aside and the case be remitted to the examining division with an order to grant a patent on the basis of the set of claims of the main request, submitted with the statement of grounds of appeal, or alternatively on the basis of the set of claims of auxiliary request 1, submitted with the letter dated 27 April 2018, or on the basis of the set of claims of auxiliary request 2, submitted as auxiliary request with the statement of grounds of appeal.

Reasons for the Decision

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

Absence of the appellant from the oral proceedings - Right to be heard (Article 113(1) EPC)

2. The appellant, who was duly summoned to the oral proceedings, announced in advance that it would not attend them. The board considered it expedient to hold the oral proceedings (Article 116(1) EPC) and decided that in accordance with Rule 115(2) EPC and Article 15(3) RPBA, they would be continued in the appellant's absence and that the appellant would be treated as relying on its written case. Hence, the appellant's right to be heard was respected (Article 113(1) EPC).

Main request

Article 76(1) EPC - process claims 8 and 9

3. The subject-matter of claims 8 and 9 relates to a process for purifying meningococcal NadA in trimeric form and comprises several steps (see section V for the complete wording of the claim).

4. The earlier application discloses a process for the purification of secreted NadA in general - comprising the same steps as recited in claim 8 - but not for the purification of secreted NadA in trimeric form specifically (see page 3, lines 13 to 17 of the earlier application).

The earlier application furthermore discloses a process for the preparation of NadA, comprising recombinant expression in *E. coli* and purification of the secreted NadA (see page 32, line 30 to page 33, line 19). In this context, it is disclosed that the NadA protein is susceptible to degradation and that degradation products can be separated from native NadA by gel filtration, which gives three peaks, wherein the first peak contains NadA aggregates and the third peak contains degradation products. The second peak is said to contain a trimeric protein, which is the desired antigen. In the board's judgement, it follows from the disclosure on page 32, line 30 to page 33, line 19 of the earlier application that a process comprising the steps as defined in present claim 8 does not lead to purified trimeric NadA.

5. The appellant submitted that the process disclosed in the earlier application does in fact lead to the production of trimeric NadA and that the gel filtration analysis merely separated the trimeric form from its aggregates and degradation products but was not a required step for preparing NadA in trimeric form.

6. However, this argument is not persuasive since the subject-matter of claim 8 is directed to a process for purifying, and not for preparing, NadA in trimeric form.

7. Therefore, the board decides that the subject-matter of claims 8 and 9 of the main request does not comply with the requirements of Article 76 EPC as a process for purifying meningococcal NadA in trimeric form from a culture supernatant without the gel filtration step is not disclosed in the earlier application.

Auxiliary request 1

Admissibility

8. This claim request was filed in direct response to the board's communication, in which an objection to process claims 8 and 9 of the main request was raised under Article 76 EPC for the first time. It differs from the main request in that the process claims have been deleted.

9. Therefore, the board decided to admit the claim request into the appeal proceedings (Articles 12(1)(c) and 13(1) RPBA).

Article 56 EPC - claim 1

Closest prior art

10. Document D2 was considered in the decision under appeal to represent the closest prior art. This was not disputed by the appellant and the board sees no reasons to disagree.

11. Document D2 discloses the expression of different forms of protein 961, including a form termed 961c-L, in *E. coli* (see page 61, line 36 to page 63, line 5). As can be seen from Figure 12, compared to the full-length protein 961, protein 961c-L lacks the membrane anchor domain.

Expression of protein 961c-L in *E. coli* yields a protein which is exported into the supernatant and is soluble (see page 62, lines 18 to 19). As the protein is present in the supernatant in soluble form, its purification is easy since it does not require cell

lysis and extraction from the membrane. That protein 961c-L induces bactericidal titres is shown in the Table bridging pages 62 and 63 of document D2 for His-fusions of 961c-L.

However, document D2, in particular the experimental data outlined on page 62, provides no evidence that protein 961c-L is in the form of oligomers, let alone trimers, when present in the supernatant.

Technical problem to be solved and its solution

12. It was not disputed by the appellant that the amino acid sequence of protein 961c-L of document D2 is the same as the amino acid sequence of protein NadA consisting of the amino acid sequence of SEQ ID NO:2 as recited in claim 1 of auxiliary request 1, corresponding to a truncated form of NadA lacking the C-terminal membrane anchor domain and the leader peptide. In the following, protein 961c-L of document D2 will be referred to alternatively as "961c-L" or "NadA".

13. The difference between protein 961c-L disclosed in document D2 and the subject-matter of claim 1 is that according to claim 1 the protein is in trimeric form.

As to the effects of the trimeric NadA protein of claim 1, the application discloses that immunisation with a preparation containing trimeric NadA induces bactericidal titres against various meningococcal strains containing the NadA gene (see page 34, lines 10 to 13 and row (3) of the first table on page 34). From pages 32, 33 and 34 it can be inferred that protein number 3 is trimeric NadA. As the monomeric constituents of the trimeric NadA complex lack the

membrane anchor domain (see point 12 above) the trimeric form is not membrane-bound, but secreted in the supernatant and thus easy to purify.

The technical effects associated with the trimeric form of NadA are thus the same effects as provided by protein 961c-L disclosed in document D2.

Hence, the technical problem to be solved is the provision of an alternative form of NadA which can be easily purified and which induces bactericidal titres.

Obviousness

14. The question to be answered when assessing the obviousness of the claimed subject-matter is whether or not the skilled person, aware of the teaching of document D2 and faced with the technical problem defined in point 13 above, would have modified the teaching of the closest prior art document D2 - possibly in the light of other prior art teachings - so as to arrive at the claimed invention in an obvious manner.

15. As mentioned above, document D2 provides no evidence for the existence in the culture supernatant of secreted NadA oligomers (see point 11 above). Indeed, the experimental data outlined on page 62 of document D2 suggest that oligomerisation of NadA requires the presence of the entire membrane anchor domain and that oligomerisation is not driven by the extracellular domain. Thus, a version of NadA with a partial deletion in the membrane anchor domain (961Δ1-L) does not form oligomers (see page 62, lines 16 to 17).

In the board's view, the skilled person would therefore understand from document D2 that any form of NadA lacking its membrane anchor domain would not form oligomers. Accordingly, the claimed solution is considered not to be obvious in view of the teaching of document D2 alone.

16. It was not contested by the appellant that the subject-matter of claim 1 is not entitled to the first claimed priority and that therefore document D5 is part of the state of the art pursuant to Article 54(2) EPC.

17. Document D5 was relied on by the examining division as disclosing that NadA can take the form of oligomers. However, document D5 relates to surface-exposed, membrane-bound, oligomers of full-length NadA (see page 25, line 17 to page 26, line 33) but not to truncated forms lacking the membrane anchor domain which are secreted into the culture medium. There is no disclosure or evidence in document D5 that a secreted version of NadA lacking the membrane anchor domain would also form oligomers, let alone trimers.

Therefore, in the board's opinion, document D5 provides no incentive for the skilled person to modify the teaching of document D2 so as to arrive at subject-matter falling within the scope of claim 1.

18. The board concludes from the above that a recombinant NadA in trimeric form wherein the NadA consists of the amino acid sequence of SEQ ID NO: 2 is neither suggested by document D2 taken alone nor when taken in combination with the disclosure of document D5, as a form of NadA which can be easily purified and which

induces bactericidal titres. Accordingly, the subject-matter of claim 1, having regard to this state of the art, is not obvious to a person skilled in the art.

Allowability of the appeal

19. The patent application was refused for lack of inventive step only. As the subject-matter of claim 1 of the present auxiliary request 1 fulfils the requirements of Article 56 EPC, the appeal is allowable and the appealed decision is to be set aside.

Remittal (Article 111(1) EPC)

20. Pursuant to Article 111(1) EPC, following the examination as to the allowability of the appeal, the board must decide on the appeal and, in this respect, it may either exercise any power within the competence of the department which was responsible for the decision or remit the case for further prosecution.

21. Since the examining division did not deal with the subject-matter of independent claim 2 or with requirements for patentability other than inventive step, the board decides to remit the case to the examining division for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division for further prosecution on the basis of the set of claims of auxiliary request 1 submitted with the letter of 27 April 2018.

The Registrar: The Chair:

P. Cremona G. Alt

Decision electronically authenticated