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Datasheet for the decision of 10 February 2015

Case Number: T 2021/11 - 3.3.04

Application Number: 07734467.9

Publication Number: 1976559

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Language of the proceedings: EN

Title of invention:
Influenza vaccines containing hemagglutinin and matrix proteins

Applicant:
Novartis Vaccines and Diagnostics GmbH

Headword:
Influenza vaccines based on a complex formed by haemaglutinin and a M1 fragment/NOVARTIS

Relevant legal provisions:
EPC Art. 54, 56, 84, 111(1), 123(2)

Keyword:
Novelty - (yes)
Inventive step - (yes)
Claim 1 - clarity (yes)
Amendments - added subject-matter (no)
Remittal to the department of first instance (yes)

Decisions cited:

Catchword:

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Case Number: T 2021/11 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 February 2015

Appellant: (Applicant)	Novartis Vaccines and Diagnostics GmbH Emil-von-Behring-Strasse 76 35041 Marburg (DE)
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 22 February 2011 refusing European patent application No. 07734467.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	M. Montrone
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The appeal was lodged by the applicant (hereinafter "appellant") against the decision of the examining division to refuse European patent application No. 07734467.9, published as international application WO 2007/085969 (hereinafter "the application as filed"). The title of the application is "*Influenza vaccines containing hemagglutinin and matrix proteins*".

II. The decision under appeal was based on a main and auxiliary requests 1 and 2. The examining division held that the subject-matter of claims 1 and 18 of the main request and claim 1 of the second auxiliary request lacked inventive step (Article 56 EPC) and that the subject-matter of claim 1 of the first auxiliary request (which corresponds to the main request in the appeal proceedings) extended beyond the content of the application as filed (Article 123(2) EPC). Regarding the latter issue, the examining division considered that the feature "haemagglutinin and a fragment with a molecular weight of ≤10kDa of Ml matrix protein, wherein the fragment comprises a T cell epitope, which form a stable complex" of claim 1 was not directly and unambiguously disclosed in the application as filed, since the sole basis for this feature on page 11, lines 3 to 4 represented "*a vague assumption that HA and M1 may form a complex but it does not represent a clear and unambiguous disclosure that the two molecules are in fact present as stable complex.*"

III. With the statement of grounds of appeal, the appellant submitted four claim requests. The main request and auxiliary requests 2 and 3 were identical to the ones before the examining division, with auxiliary request 3

corresponding to auxiliary request 1 in the examination proceedings.

IV. In a communication pursuant to Article 15(1) RPBA the board expressed its preliminary view that the subject-matter of claim 18 of the main request lacked novelty over the disclosure of document D1 (the respective document is identified in section VI below). It also informed the appellant that the subject-matter of claim 1 of the third auxiliary request seemed to comply with the requirements of Article 123(2) EPC and that remittal to the examining division was envisaged.

V. Oral proceedings before the board took place on 10 February 2015. During the oral proceedings the appellant changed the order of the claim requests submitted with the statement of grounds of appeal, i.e. making its former auxiliary request 3 its new main request.

Claim 1 of the new main request reads:

"1. A purified surface antigen or split virion influenza vaccine, comprising influenza virus haemagglutinin and a fragment with a molecular weight of ≤10kDa of Ml matrix protein, wherein the fragment comprises a T cell epitope, which form a stable complex, and wherein the composition does not contain ovalbumin."

VI. The following documents are cited in this decision:

D1: Galarza et al., Viral Immunol., 2005, vol. 18(1), p. 244-251

D2: EP0870508

D4: Plotnicky et al., Virology, 2003, vol. 309, p. 320-329

D11: Brands et al., Dev. Biol. Stand., 1999, vol. 98, p. 93-100

D14: Johansson et al., Virology, 1996, vol. 225, p. 136-144

VII. The appellant's arguments may be summarised as follows:

Main Request

Article 123(2) EPC

The feature in claim 1 that haemagglutinin (HA) and matrix 1 protein (M1) fragments having a size of ≤10kDa formed a stable complex was disclosed on page 11, lines 3 and 4 in combination with the disclosure on page 10, line 23 of the application as filed.

Article 84 EPC

The feature "form a stable complex" of claim 1 was a standard term in the art and its meaning thus clear for the skilled person.

Article 56 EPC

The disclosure of documents D2 or D11 represented the closest prior art for the subject-matter of claim 1. These documents disclosed a cell culture-derived influenza virus vaccine based on the purified surface antigens HA and neuraminidase (NA), but such a vaccine disclosed neither M1 or fragments thereof nor that M1

fragments of ≤10kDa with a T-cell epitope formed a stable complex with HA.

The presence of a complex of HA and the M1 fragments resulted in an improved cross-protective efficacy of the vaccine according to claim 1, i.e. a protective immune response against different influenza strains through "cognate help". This phenomenon *per se* was known and depended on the presence of physically associated viral antigens that strongly activated cytotoxic T-cells (CTLs) which, if they were directed against a conservative viral antigen such as M1, were responsible for the improved cross-protection. The activated T-cells also stimulated B-cells in the production of antigen-specific antibodies.

That the claimed vaccine composition achieved this improvement was credible in view of the common general knowledge of the skilled person derivable from the teaching of document D14.

A further advantage associated with the spontaneous formation of a stable complex of HA and M1 fragments was easier manufacturing of the vaccine claimed.

The objective technical problem was thus the provision of an influenza virus vaccine composition having improved cross-protective efficacy that was obtained by a simplified manufacturing process.

Cognate help depended on the presence of stably associated antigens (see document D14). The finding of the application that M1 fragments of ≤10kDa formed a stable complex with HA was surprising in view of the prior art, which only taught a complex formation between HA and M1 if both proteins were present at

their full length (see documents D1 or D14). This complex formation occurred under specific conditions, namely only when M1 fragments of ≤10kDa were co-purified with HA but not if both components were individually purified and then mixed only afterwards.

The skilled person would therefore not have arrived at the subject-matter of claim 1 in an obvious manner. Consequently, it was inventive.

VIII. The appellant requested that the decision under appeal be set aside and that the case be remitted to the department of first instance with the order to grant a patent on the basis of the main request or one of auxiliary requests 1 to 3 (all filed during the oral proceedings).

Reasons for the Decision

Main Request

Amendments (Article 123(2) EPC)

1. It is established case law that amendments are permitted within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, from the disclosure of the application as filed as a whole (see Case Law of the Boards of Appeal, 7th edition, II.E.1, page 361, fourth paragraph).

Claim 1

2. Claim 1 relates to a purified surface antigen or split virion influenza virus vaccine from virions grown in cell culture which comprises the following features:

(i) an influenza haemagglutinin (HA); and

(ii) a fragment with a molecular weight of ≤10kDa of Ml matrix protein, wherein the fragment comprises a T cell epitope;

(iii) wherein the HA and the M1 fragments form a stable complex; and

(iv) wherein the composition is free of ovalbumin (OVA).

3. The application as filed reads on page 2, lines 24 to 27 as follows: "*The invention does not use a whole virion (WV) antigen* [...]*. Instead, the antigens of the invention are non-WV antigens, such as split virions, or purified surface antigens. Compositions of the invention comprise at least two influenza virus antigens: haemagglutinin and matrix.*"

3.1 This passage explicitly discloses a purified surface antigen or split virion influenza vaccine which comprises HA and a matrix (M) protein (i.e. feature (i) above).

3.2 M1 fragments of ≤10kDa, as preferred M proteins, are disclosed on page 10, lines 20 to 23: "*Thus preferred matrix proteins included in compositions of the invention* include one or more of the amino acid sequences SEQ ID NOs: 1, 21, 22, 23, 24, 25, 26 and or 27. *Whereas full-length* ***M1*** *protein is a 27.8kDa protein, however, the* ***matrix protein included in the compositions of the invention*** *is* [*sic*] *has a molecular weight of <20kDa e.g. ≤15kDa, ≤12kDa,* ***≤10kDa***" (emphasis added by the board). That the M1 fragment comprises a

T-cell epitope is derivable from page 9, lines 13 and 14 (i.e. feature (ii) above).

3.3 The application reads on page 11, lines 3 to 5: "*Without wishing to be bound by theory, the inventors believe that matrix proteins may bind to HA in a vaccine to form a stable complex*" (i.e. feature (iii) above). The examining division argued that this sentence represented "*a vague assumption that HA and M1 fragments may form a complex but it does not represent a clear and unambiguous disclosure that the two molecules are in fact present as a stable complex*" (see section II above).

The assessment of the compliance of amendments with the requirements of Article 123(2) EPC requires establishing the information content conveyed to the skilled person by the disclosure of the application. In the board's view, the skilled person would understand from the sentence cited above that M1 and HA form a stable complex. Whether this is true in reality, i.e. whether a complex between the two molecules is indeed formed, is not relevant for the assessment of Article 123(2) EPC. Hence, the board considers that feature (iii) above is explicitly disclosed in the above cited sentence.

3.4 Lastly, feature (iv) above, i.e. that the immunogenic composition of the invention is free of OVA, is derivable from claim 2 as filed.

4. The subject-matter of claim 1 thus has a basis in the application as filed.

Claims 2 to 16

5. The examining division has not raised objections pursuant to Article 123(2) EPC against the subject-matter of claims 2 to 16.

6. The board has none either, since the subject-matter of claims 2 and 3 is disclosed on page 10, line 25 and that of claim 4 on page 9, lines 22 and 23 of the application as filed. Moreover, the subject-matter of claims 5 to 16 corresponds to that of claims 6, 8, 10, 13, 11, 12, 14, 15, 17, 19, 20 and 22 as filed, respectively.

7. The board therefore concludes that the subject-matter of claims 1 to 16 meets the requirements of Article 123(2) EPC.

Clarity, support (Article 84 EPC)

Claim 1

8. The board has no objections and is in particular satisfied that the protein antigens of claim 1 are generally known in the art (see page 1, lines 7 to 16 and page 8, lines 16 to 18 of the application as filed) and that a stable complex formation between HA and M1 fragments of a certain size can be readily tested by the person skilled in the art. The subject-matter of claim 1 thus fulfils the requirements of Article 84 EPC.

Novelty (Article 54 EPC)

9. A cell culture-derived influenza virus vaccine according to claim 1 is not disclosed in any of the prior art documents on file. The board therefore concludes that the subject-matter of claim 1 is novel. This conclusion also applies to the subject-matter of claims 2 to 16 which are all dependent on claim 1.

10. Hence, the subject-matter of claims 1 to 16 meets the requirements of Article 54 EPC.

Inventive step (Article 56 EPC)

Closest prior art

11. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the Boards of Appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art. In accordance with the established case law, the closest prior art is generally a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention (see Case Law of the Boards of Appeal, 7th edition 2013, I.D.3.1).

12. Both the examining division and the appellant considered that the disclosure of either document D2 or D11 represented the closest prior art for the subject-matter of claim 1.

13. The board notes that both documents aim at the provision of ovalbumin-free, MDCK cell culture-derived purified influenza virus surface antigens for the preparation of a vaccine comprising HA and neuraminidase (NA) (see document D2, abstract and page 3, line 6; document D11, abstract, page 94, last paragraph to page 95, first paragraph, page 96, last paragraph) and therefore relate to the same purpose as the present invention, i.e. the provision of a vaccine against influenza virus infection.

However, document D11 discloses that the vaccine contains "*predominantly HA and NA*" (see page 96, last paragraph), which implies the presence of further undefined viral proteins. Document D2, in contrast, relates to an influenza virus vaccine derived from cell culture which comprises surface antigens and thus only HA and NA (see page 3, line 1).

Document D11 therefore has more technical features in common with the subject-matter of claim 1 than document D2. Accordingly, the board concludes that the purified surface antigen composition of document D11 represents the closest prior art in accordance with the case law (see point 11 above).

Technical problem and solution

14. The vaccine composition of claim 1 differs from that of the closest prior art in that it comprises an M1 matrix protein fragment of a size of ≤10kDa which comprises a T-cell epitope and forms a stable complex with HA.

Matrix proteins with T-cell epitopes are immunologically conserved influenza virus antigens which can induce cross-protection, i.e. a T-cell-based

immunity against different viral HA types (see page 10, lines 34 to 36 of the application as filed).

The cross-protectivity of matrix proteins is improved if they form a stable physical association with HA because this antigen complex induces a so-called "cognate help" immune response. This means that T-cells are far more strongly activated than if the antigens are individually administered (see document D14, figure 2C; page 139, column 1, second paragraph, and page 141, column 1, first paragraph). This activation of T-cells results on the one hand in a more efficient lysis of cells infected by the different viral subtypes through cytotoxic T-cells (CTLs) and on the other hand in T-cells that stimulate B-cells to produce antigen-specific antibodies (see document D14, page 142, column 1, third paragraph, figures 2B, 2C).

15. Accordingly, in view of the closest prior art and in view of the effects achieved by the claimed composition, the technical problem to be solved is formulated as the provision of an influenza virus vaccine with improved cross-protection.

16. The board is satisfied that this problem is credibly solved by the vaccine composition of claim 1 in view of the common general knowledge derivable from document D14, which reports that M1 proteins are highly conserved between different influenza virus subtypes and that stably associated influenza virus antigens induce a cognate help response which increases the T-cell-dependent cross-protection (see page 142, column 1, third paragraph to column 2, second paragraph).

Obviousness

17. The question to be answered is whether the skilled person, starting from the vaccine composition of document D11 and faced with the technical problem defined in point 15 above, would be motivated to provide the claimed vaccine combination in the light of the teaching of document D11 alone or in combination with the teaching of either of documents D14, D1 or D4.

18. As noted above, document D11 alludes to the presence of proteins other than HA and NA in an influenza virus vaccine composition by stating that it comprises "*predominantly HA and NA*". It does not, however, hint at matrix proteins such as M1 protein or fragments thereof, let alone an M1 fragment of ≤10kDa complexed with HA. Moreover, this document is silent about the possible cross-protective potential of the influenza virus vaccine disclosed and how the cross-protectivity could be improved.

19. Therefore, the subject-matter of claim 1 is not obvious in the light of the teaching of document D11 alone.

20. Document D14 reports on a study comparing the effects of dissociated M1 protein and nucleoprotein (NP), i.e. internal influenza viral antigens, or a whole inactivated influenza virus on the immune response towards the surface antigens HA and NA. The authors conclude that "*effective influenza vaccines need* ***not*** *contain internal viral antigens although we have demonstrated the capacity of these antigens to prime M1/NP specific B-cell and T-cell population*" (see page 143, column 1, lines 12 to 15; emphasis added by the board).

21. Thus, document D14 does not suggest including M1 matrix proteins in an influenza virus vaccine composition.

22. Document D1 reports on a stable physical association between the two **full-length** proteins HA and M1 in the form of a virus-like particle (VLP) that forms spontaneously upon recombinant production in insect cells (see abstract; page 246, column 1, fourth paragraph).

23. Thus, the document discloses an influenza virus vaccine which is conceptually different from the vaccine referred to in claim 1, i.e. one comprising a purified surface antigen or a split virion. It moreover does not point to the inclusion of an M1 fragment complexed to HA, let alone that it suggests that fragments of M1 are able to stably bind to HA.

24. Finally, document D4 discloses a study based on an immunodominant M1 peptide epitope (M1 protein amino acid positions 58-66) that induces a cross-protective CTL response in immunised mice against different influenza strains (see page 320, abstract; page 326, column 1, last paragraph). Regarding the cross-protectivity of influenza virus vaccines the authors state that "*In the case of influenza, it is formerly assumed that most of the cross-protection observed against different strains of viruses relies on the activity of cytotoxic T cells [...]. It would thus be particularly interesting to identify the epitopes derived from internal proteins which are less abundant to the infected cell surface but also less variable than HA or NA, to design a vaccine*" (see page 326, column 1 third paragraph).

25. In the board's view, the skilled person would derive from the teaching of document D4 that the influenza virus vaccine is to be based solely on the M1 peptide specifically disclosed, or on other peptide epitopes of internal proteins, such as M1. According to document D4 the presence of this peptide epitope would be sufficient to induce a cross-protective immune response. Ways of improving the cross-protectivity of such a vaccine are not suggested to the skilled person. The document also contains no hint for the skilled person to combine the M1 peptide with HA in a vaccine, let alone to bind this peptide to HA to improve the cross-protective potential of an influenza virus vaccine.

26. In summary, the board concludes that document D11 even in combination with the teaching of either of documents D14, D1 or D4 does not give any motivation to the skilled person to solve the technical problem formulated above in point 15 by providing a stable complex of HA with M1 fragments having a molecular weight of ≤10kDa and containing a T-cell epitope.

27. Hence, the subject-matter of claim 1 is not obvious. This conclusion applies also to the subject-matter of claims 2 to 16 which are all dependent on claim 1.

28. Thus, the requirements of Article 56 EPC are fulfilled.

Remittal (Article 111(1) EPC)

29. Pursuant to Article 111(1) EPC, having examined the allowability of the appeal, the board decides 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 appealed or remit the case to that department for further prosecution.

30. During the examination proceedings the examining division has never taken position with regard to the requirements of Article 83 EPC. For this reason, the board decides to exercise its discretion under Article 111(1) EPC and to remit the case to the examining division for further prosecution.

31. During this further prosecution the examining division will need to assess the requirements of Article 83 EPC in particular as to whether the application discloses the feature in claim 1 "wherein the HA and the M1 fragments of ≤10kDa form a stable complex" in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Furthermore the requirements of Article 84 EPC will have to be examined with regard to claims 2 to 16 (see point 8 above).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated