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Datasheet for the decision of 26 May 2010

Case Number: T 0640/06 - 3.3.04

Application Number: 99961935.6

Publication Number: 1135408

IPC: C07K 14/02

Language of the proceedings: EN

Title of invention:
HBV core antigen particles with multiple immunogenic components attached via peptide ligands

Applicant:
Biogen Idec MA Inc.

Headword:
HBV particles/BIOGEN IDEC

Relevant legal provisions:
EPC Art. 54, 56, 83, 84

Keyword:
"Added subject-matter (no)"
"Clarity (yes)"
"Sufficiency of disclosure (yes)"
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0640/06 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 26 May 2010

Appellant: Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, Massachusetts 02142 (US)

Representative: von Menges, Albrecht Dr.
UEXKÜLL & STOLBERG
Patentanwälte
Beselerstrasse 4
D-22607 Hamburg (DE)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 8 December 2005 refusing European patent application No. 99961935.6 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: M. Wieser
Members: R. Gramaglia
R. Moufang

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division, whereby the European patent application No. 99961935.6 (published as WO-A-00/32625) having the title "HBV core antigen particles with multiple immunogenic components attached via peptide ligands" was refused pursuant to Article 97(1) EPC 1973. The decision under appeal was based on a set of 57 claims filed on 2 September 2003, of which claims 1, 3 and 4 read as follows:

"1. An HBV core antigen particle having multiple immunogen specificities, said particle comprising at least one capsid binding immunogen, said capsid binding immunogen comprising at least one HBV capsid—binding peptide component and at least one immunogenic component."

"3. The HBV core antigen particle according to claim 1, wherein said capsid binding immunogen is linked to said particle through any amino acid residue of said HBV capsid—binding peptide component."

"4. The HBV core antigen particle according to claim 1, wherein said capsid binding immunogen is linked to said particle through any amino acid residue or other residue of said immunogenic component."

II. The reasons for the rejection were lack of novelty, lack of clarity and insufficiency of disclosure of the claims then on file.

III. With a statement of grounds of appeal filed on 10 April 2006, the appellant submitted a new set of 57 claims.

IV. In communications dated 16 January 2009, 22 January 2009 and 25 March 2010, the board expressed its preliminary opinion.

V. With letter dated 29 January 2009 the appellant submitted an amended set of claims 1-49 and amended pages 1, 5, 6, 8, 9, 33 and 40 of the description and withdrew its request for oral proceedings, unless the board intended to raise additional objections or to maintain any of the previous objections. The set of claims above was replaced by claims 1-49 filed with the letter dated 29 April 2010. Claims 1 and 3 of the new set of claims read as follows:

"1. An HBV core antigen particle having multiple immunogen specificities, said particle comprising at least one capsid—binding immunogen, said capsid-binding immunogen comprising at least one HBV capsid-binding peptide component and at least one immunogenic component, wherein the HBV capsid-binding peptide is used to non-covalently link the immunogen to the HBV core antigen particle."

"3. An HBV core antigen particle having multiple immunogen specificities, said particle comprising at least one capsid-binding immunogen, said capsid-binding immunogen comprising at least one HBV capsid-binding peptide component and at least one immunogenic component, obtainable by using the HBV capsid-binding peptide to link the immunogen non-covalently to the HBV core antigen particle and subsequently binding the

capsid—binding immunogen covalently to said particle through any amino acid residue of said HBV capsid-binding peptide component or of said immunogenic component."

Claims 2, 4 to 32, 36 and 47 relate to specific embodiments of the HBV core antigen particles according to claim 1. Independent claims 33, 34 and 35 relate to a vaccine, a pharmaceutical composition and a method for increasing the immunogenicity, respectively. Claim 37 covers a diagnostic method involving the particles according to claim 36. Claim 38 is addressed to a capsid-binding peptide immunogen comprising at least one capsid-binding peptide and at least one immunogenic component. Claims 39 to 46 relate to specific embodiments of the capsid-binding peptide immunogen according to claim 38. Claims 48 and 49 cover a use of the HBV core antigen particles according to claims 1 to 32.

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

D1 Böttcher B. et al., EMBO Journal, Vol. 17, No. 23, pages 6839-6845 (December 1998);

D2 Schödel F. et al., J. of Biotechnology, Vol. 44, pages 91-96 (1996);

D3 Ulrich R. et al., Advances in Virus Research, Vol. 50, pages 141-182 (1998).

VII. The submissions by the appellant (applicant), insofar as they are relevant to the present decision, can be summarized as follows:

Article 123(2) EPC

- Claim 1 was amended to clarify that the HBV capsid-binding peptide was non-covalently linked to the HBV core antigen particle.

- Claim 3 specified the two-step method involved in obtaining the HBV core antigen particles of the present invention. The first step comprised the non-covalent link between the HBV capsid-binding peptide and the HBV core antigen particle and the second step comprised the covalent link between the complex of the HBV core antigen particle and HBV capsid-binding immunogen. The fact that the methods used to generate the claimed HBV core antigen particles were two-step methods was disclosed in the application on page 22, lines 22-25 and in Example 2 (see page 38, lines 7-12).

- Claims 4 to 6 were amended to specify the covalent reaction linking the capsid-binding immunogen to the HBV core particle as the second step of the two-step process.

- Claim 35 was amended by specifying that the linking occurred in a non-covalent manner.

- Claim 38 incorporated the immunogens listed in former claims 40 to 46.

– All the amendments above were supported by the application as filed and were thus in compliance with Article 123(2) EPC.

Sufficiency of disclosure (Article 83 EPC)

– The objection under this Article raised by the department of first instance had not been substantiated.

Novelty (Article 54 EPC)

– Document D1 did not teach HBV core antigen particles having multiple immunogen specificities which comprised at least one capsid binding immunogen which, in turn, included at least one HBV capsid-binding peptide component and at least one immunogenic component. Instead, document D1 referred to HBV core antigen particles comprising only an HBV capsid-binding peptide, without an additional immunogenic component linked to that peptide.

Inventive step (Article 56 EPC)

– The prior art (documents D1 and D2) taught completely different fusion polypeptides. Therefore, the skilled person could not have derived the claimed subject matter from the prior art without inventive skills.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the amended set of claims filed with the letter

dated 29 April 2010 and the amended description submitted with the letter dated 29 January 2009.

Reasons for the Decision

Clarity (Article 84 EPC)

The claims before the examining division

1. The examining division concluded that the expression "HBV core antigen particle" in the claims then on file (see Section I supra) rendered the claims unclear. This lack of clarity followed, in the examining division's view, inter alia, from a discrepancy between claims 3 and 1 then on file (see point 7 of the decision under appeal: "However, according to claim 3, the "capsid binding immunogen" is linked to "said particle" and, thus, cannot, as required by claim 1, be comprised **in** the particle"; emphasis by the board).

2. However, claim 1 then before the examining division merely stated "said particle comprising at least one capsid binding immunogen", without specifying where. Once interpreting the claim in the light of Fig. 1 as filed, it becomes evident that said "capsid binding immunogen" is **on** (rather that in) the particle, the more so as "buried" antigens are known to be of little interest when it comes to eliciting an immune response (see page 20, lines 17-21). This interpretation of claim 1 as meaning that the "capsid binding immunogen" is located within the particle thus runs against the common sense and hence the board sees no discrepancy between claims 1 and 3 on the grounds pointed out by the examining division.

3. Moreover, it is true that the present application gives two different meanings for the expression "HBV core antigen particle" in claim 1, namely (i) that of "particles obtained from multimerization of the HBV core antigen protein (and carrying no foreign epitopes)" (see page 9, line 32 to page 10, line 27 of the application; see also page 36, first paragraph, relating to a prior art method for preparing such particles), and (ii) that of "core particles of HB virus carrying foreign epitopes" (see the chapter headed "Properties of the Resulting HBV Core Antigen Particles" starting from page 38). However, the skilled person would understand that the expression "HBV core antigen particle" when used in line 1 of claim 1 relates to "core particles of HB virus carrying foreign epitopes", whereas, when used in the subordinate clause of claim 1, relates to particles obtained from multimerization of the HBV core antigen protein.

4. In point 8 of the decision under appeal, the examining division concluded that the term "capsid binding immunogen" represented an attempt to define a technical feature in terms of the result to be achieved, rather than in terms of structural information, thus rendering the claims unclear.

5. The board, however, is of the opinion that the skilled person would understand that this term relates to any immunogen capable of binding to the "HBV core antigen particle" via a capsid-binding peptide. In other words, a "capsid binding immunogen" comprises two components, namely a capsid-binding peptide linked to an immunogen (see the application on page 6, lines 24-26 and on

page 27, line 1 to page 28, line 5 and in Figure 1). As regards the immunogen, a list of possible immunogens can be found on pages 8 and 9 of the application. As for the "capsid-binding peptide", this term is already defined in the prior art as being a peptide which binds with high affinity to shells (particles) consisting of the full-length core protein (see document D1, page 6840, l-h column, lines 10-12). The application, under the paragraph headed "HBV Capsid-Binding Peptides Used to Ligate Immunogens to the HBV Core Antigen Particles" (see pages 20-26), describes in detail how these peptides can be prepared and which properties they should exhibit, e.g. a high affinity for the HBV core antigen (see page 24, line 5) and the presence of two conserved basic residues capable of binding to the two acidic residues Glu^{77} and Asp^{78} situated at the tips of the spikes of the HBV core particles (see page 11, line 24 to page 12, line 4). In view of the ample information provided by the application, the wording "capsid binding immunogen" can be seen neither as a functional definition, nor as an invitation to perform an arduous search for identifying and preparing molecules which behave as "capsid binding immunogens", as the examining division maintained.

6. In conclusion, the objections under Article 84 EPC raised by the examining division in points 7 and 8 of the decision under appeal were not justified.

The claims before the board

7. By comparison with claim 1 refused by the examining division (see Section I supra), present claim 1 comprises the wording "wherein the HBV capsid-binding

peptide is used to non-covalently link the immunogen to the HBV core antigen particle". This wording specifies that (i) the HBV capsid-binding peptide acts as a ligand (bridge) to immobilize the immunogen onto the HBV core antigen particle and that (ii) the bond which is formed between the peptide and the particle is of a non-covalent nature (c.f. "non-covalently"), i.e., it occurs by means of interaction between electric charges of opposed sign (peptide: positive; spikes: negative). Moreover, the presence of two conserved basic residues capable of binding to the two acidic residues Glu^{77} and Asp^{78} situated at the tips of the spikes of the HBV core particles (see page 11, line 24 to page 12, line 4), ensures that the HBV capsid-binding peptide and hence the capsid binding immunogen targets the tips of the spikes of the HBV core particles (see page 22, lines 23-25 of the application).

8. Claim 3 (first step) also specifies that the linking occurs in a non-covalent manner. Therefore, the HBV capsid-binding peptide and hence the capsid binding immunogen is automatically directed towards the tips of the spikes of the HBV core particles, where it is successively "freezed" by covalent binding (second step).

Claim 35 also specifies that the linking occurs in a non-covalent manner.

9. With the present claims formulation, the clarity problems encountered by the department of first instance, even assuming they were justified, no longer arise.

10. Therefore, the claims satisfy the requirements of Article 84 EPC.

Article 123(2) EPC

11. Claim 1 refused by the examining division (see Section I supra), merely differs from original claim 1 by the expression "having multiple immunogen specificities" in the former. This wording, having a basis on e.g., page 1, line 7 of the WO application as filed, does not introduce added subject-matter. As highlighted under point 2 supra, claim 1 before the examining division (and hence claim 1 as originally filed) required that the "capsid binding immunogen" had to be somewhere on the "HBV core antigen particle", without specifying what bond (covalent via electron sharing or non-covalent, via interaction between electric charges of opposed signs) held the two entities together.

12. By comparison with claim 1 refused by the examining division, present claim 1 now further comprises the wording "wherein the HBV capsid-binding peptide is used to non-covalently link the immunogen to the HBV core antigen particle". Otherwise stated, this wording now specifies that (i) the HBV capsid-binding peptide acts as a ligand (bridge) to immobilize the immunogen onto the HBV core antigen particle and that (ii) the bond which forms between the peptide and the particle is of a non-covalent nature (c.f. "non-covalently"), i.e., it occurs by means of interaction between electric charges of opposed sign. This amendment is supported by page 22, lines 22-25 and by page 11, line 20 to page 12, line 4 of the WO application as filed, from which it can be

derived that binding of the immunogen occurs via the HBV capsid-binding peptide acting as a ligand (page 25, lines 2-4) having affinity for the HBV core antigen particles (page 24, line 5). A complex is formed (see page 37, line 4) owing to the electrostatic interaction between, on the one hand, the two (negatively charged) acidic residues Glu^{77} and Asp^{78} situated at the tips of the spikes of the HBV core particles and, on the other hand, two (positively charged) basic residues of the peptide. And in fact, all the peptides listed on pages 23 and 24 of the WO application include the motif -RMK- (or in the three-letter code -Arg-Met-Lys-) comprising the two basic residues Arg and Lys.

13. In conclusion, present claim 1 does not infringe Article 123(2) EPC.

14. Independent claim 3 relates to the embodiments of claims 3 and 4 before the examining division (see paragraph I supra), wherein the HBV core antigen particle having multiple immunogen specificities is made through a two-step method. The first step comprises the non-covalent binding of the immunogen to the HBV core antigen via the HBV capsid-binding peptide, the latter acting as a ligand by virtue of the electrostatic interaction (see point 12 supra) and the second step consists in chemically cross-linking ("freezing") the complex between the HBV core antigen particle and the HBV capsid-binding immunogen through any amino acid residue of said HBV capsid-binding peptide component (former claim 3) or of said immunogenic component (former claim 4). This two-step method is disclosed in the WO application (see for example page 28, the Chapter headed "Linkage of Capsid-

Binding Immunogens to the HBV Core Antigen Particle"; see also Example 2, page 38, lines 7-12, where it is stated that "These peptides, and the basic HBV capsid-binding peptide ... were bound to an HBV core antigen particle ... and cross-linked with EDC or sulfo-NHS").

15. Claims 4 to 6 correspond to claims 6 to 8 as originally filed, with an amendment to specify the covalent reaction linking the capsid-binding immunogen to the HBV core particle as the second step of the two-step process. Such an amendment has a basis in the description (see preceding point).

16. Claim 33, like claim 35 as filed, is directed to vaccines comprising HBV core antigen particles according to claim 1. Since the amendment made in present claim 1, compared to original claim 1, does not add subject-matter (see points 12 and 13 supra), this conclusion extends to present claim 33.

17. Claim 34, like claim 36 as filed, is directed to pharmaceutical composition comprising HBV core antigen particles according to claim 1. Since the amendment made in present claim 1, compared to original claim 1, does not add subject-matter (see points 12 and 13 supra), this conclusion extends to present claim 34.

18. Claim 35 corresponds to claim 39 as originally filed, with an amendment specifying that the linking occurs in a non-covalent manner. Such an amendment has a basis in the description (see points 12 and 13 supra).

19. Claim 38 incorporates the immunogens listed in claims 40 to 46 refused by the examining division.

These immunogens were also listed in original claims 51 to 56.

20. Consequently, all the amendments above are supported by the application as filed and are thus in compliance with Article 123(2) EPC.

Sufficiency of disclosure (Article 83 EPC)

21. In point 8 of the decision under appeal, the examining division concluded that the description "does not enable the skilled person to carry out such an invention over the whole scope of the claims without undue burden (Article 83 EPC)", without giving any detailed reasons for its negative finding.

22. The board, however, observes that the application, under the paragraph headed "HBV Capsid-Binding Peptides Used to Ligate Immunogens to the HBV Core Antigens Particles" (see pages 20-26) describes in detail how capsid binding peptides can be prepared. Page 10, lines 14 to 27 of the application also provides the technical information as to how HBV core antigen particles can be obtained. Reference is also made on page 36, first paragraph, to a prior art method for preparing such particles. Furthermore, the chapters headed "Linkage of HBV Capsid-binding Immunogens" (pages 26-28) and "Linkage of the Capsid-binding Immunogens to the HBV Core Antigen Particle" (page 28) provide instructions as to how the linkages should be performed. The skilled person is thus in a position to arrive without undue burden at the claimed particles having multiple antigen specificities.

23. As regards the vaccine, the pharmaceutical composition and the method for increasing the immunogenicity according to independent claims 33, 34 and 35, respectively, the board finds it credible that the claimed particles having multiple antigen specificities achieve enhanced immunogen presentation for the reasons pointed out on page 7, lines 16-30 of the WO application. Moreover, in the case of non-covalent binding of the HBV capsid-binding peptide to the particle, the skilled person would select (e.g., from the tables on page 23-24 of the application) peptides having a sufficiently high affinity for the HBV core antigen (namely, low K_D or IC_{50}). For instance, document D1 (see page 6840, l-h column, line 11) qualifies peptide GSLLGRMKGA having an IC_{50} = 0.79 µM (see list on page 24) as having "high affinity for HBcAg".

24. Therefore, in the absence of any facts that would support a finding of insufficiency of disclosure, the board is satisfied that the claimed subject matter meets the requirements of Article 83 EPC.

Novelty (Article 54 EPC)

Document D1

25. In order to deny novelty, the examining division reasoned that document D1 disclosed on page 6841, l-h column, first paragraph a HBV core antigen particle comprising a "capsid-binding immunogen" constituted of a capsid-binding peptide, i.e., the peptide MHRSLLGRMKGA, cross-linked to an immunogenic component having multiple specificities.

The board acknowledges that page 6841, l-h column, first paragraph of document D1 describes the cross-linking by means of EDC and sulfo-NHS of the capsid-binding peptide MHRSLLGRMKGA to HBV core antigen particles. However, this process merely results in HBV core antigen particles bearing a HBV capsid-binding peptide **devoid** of the additional immunogenic component linked to that peptide, contrary to the requirements of claim 1 (see paragraph V supra) that said immunogenic component should be present and should be linked to the HBV core antigen particle via the HBV capsid-binding peptide.

Document D2

26. This document fails to mention any capsid-binding peptide, let alone an HBV core antigen particle having multiple immunogen specificities, wherein said HBV capsid-binding peptide is used to non-covalently link the immunogen to the HBV core antigen particle.

27. In summary none of documents D1 or D2 is novelty-destroying for the subject-matter of present claim 1 or of independent claim 3. This conclusion extends to claims 2, 4 to 37 and 47 to 49, all relying on the HBV core antigen particles having multiple immunogen specificities according to claims 1 or 3. Nor are these documents novelty-destroying for the capsid-binding peptide immunogen comprising at least one capsid-binding peptide and at least one immunogenic component according to claim 38 and dependent claims 39 to 46.

Inventive step (Article 56 EPC)

28. The examining division dealt with this issue in the communication dated 12 June 2003, stating that the deficiencies mentioned in the international preliminary examination report (IPER) gave rise to objections under the corresponding provisions of the EPC. In said IPER, under Section V, it was stated that claims 1-60 lacked an inventive step, however, without giving any reasons for this negative finding.

29. In its communication dated 16 January 2009, expressing its preliminary opinion, the board pointed out that the feature that the capsid binding peptides had to target the tips of the spikes of the HBV core antigen particles (see page 22, lines 23-25 of the WO application) could not be derived from the claims submitted with the statement of grounds of appeal. The board's preliminary opinion, however, emphasized that this feature was critical for distinguishing over the prior art (see point 36 infra).

30. The claims presently before the board, comprising the feature outlined above (see point 7 supra), remedy this deficiency.

Closest prior art

31. The claimed subject matter relates to immunogenic nucleocapsid particles, namely HBV core antigens particles bearing immunogens.

Document D1

32. Document D1 investigates on the binding sites for oligopeptides carrying the motif -LLGRMK- and shows that peptides including this sequence can block hepatitis B virus assembly by binding to the HBV core antigen. The analysis indeed revealed that the tips of the spikes of the core protein were the binding sites for one of such peptide (GSLLGRMKGA). In summary, the experiments described in document D1 do not aim at providing HBV antigen particles to be used as carriers for immunogens, but rather at providing therapeutic agents (see page 6843, r-h column, last line of "Discussion") for inhibiting virus assembly (see page 6842-6843, the chapter headed "Peptide reduces virus yield from transfected cells").

Document D2

33. This document deals with the use of HBV core antigen particles as vaccine carrier moieties for antigens, such as the circumsporozoite (CS) antigen repeat epitopes of P. berghei, P. yoelii or P. falciparum ("P." = Plasmodium). The binding of these antigens to the particles occurs by multimerization of fusion proteins comprising the HBV core antigen and the Plasmodium CS antigens.

Document D3

34. This document (see pages 151-164) reviews the use of HBV core antigen particles as a vaccine carrier moieties for various antigens, inserted in fusion proteins. Although document D3 is mainly concerned with

exposition of the antigens on the particles' surface via fusion proteins, it is stated on page 146, line 1, of this document that grafting of foreign epitopes on the viral proteins of Table I of document D3 (including HBV HBcAg) may also occur "by chemical linkage" (i.e., covalent cross-linking), in addition to genetic engineering (involving fusion proteins).

35. The claimed subject matter involves linking foreign epitopes (immunogens) to the particles via a non-covalent (claim 1) or a covalent bond (claim 3). Therefore, document D3 (see especially page 146) relating to covalent cross-linking of immunogens to viral particles is considered by the board to represent the closest prior art.

Problem to be solved

36. The covalent cross-linking approach referred to in document D3 occurred **randomly** between any adjacent primary amino and carboxy groups (see e.g., the prior art cited in the present application, on page 36, lines 20-23), whereas according to the invention, the capsid binding immunogen targets the tips of the spikes of the HBV core particles by virtue of the "guiding" effect of the HBV capsid-binding peptide acting as a ligand (see point 7 supra). The objective technical problem underlying the present invention thus resides in providing an alternative way of linking immunogens to HBV core antigen particles.

37. Starting from document D3, in the board's view, the solution proposed in present claim 1 and 3 is rendered

obvious neither by any of documents D2 or D3 taken alone, nor by their combination with document D1.

38. As outlined in more detail above, document D2 teaches a different solution (the "fusion protein" approach) to the problem underlying the present invention and contains no pointer to the claimed solution. Document D3 refers to random chemical cross-linking and does not suggest how to solve the problem of specifically targeting the tips of the spikes.

39. As for document D1, it deals with solving a different problem, namely to identify peptides which inhibit HBV virus assembly by binding to the HBV core antigen and thus preventing the association of the core antigen with HBV surface antigen. The experiments described in document D1 are thus not aimed at providing an HBV antigen particle as an immunogen. Hence, the skilled person wishing to solve the problem of providing an alternative way of linking immunogens to HBV core antigen particles would not have turned to document D1 or combined the disclosure of document D2 and/or D3 with that of document D1.

40. Therefore, the board is satisfied that the subject-matter of claim 1 and 3 meets the requirements of Article 56 EPC. This conclusion extends to the remaining claims.

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 the following documents:

Claims: 1-49 filed with the letter dated 29 April 2010

Description: pages 2-4, 7, 10-32 and 34-39 of the published WO application
pages 1, 5, 6, 8, 9, 33 and 40 filed with the letter dated 29 January 2009

Drawings: 1/2 to 2/2 as filed.

The Registrar: Chair:

P. Cremona M. Wieser