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Datasheet for the decision of 28 November 2018

Case Number: T 2290/15 - 3.3.04

Application Number: 11075205.2

Publication Number: 2394657

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Language of the proceedings: EN

Title of invention:
Vaccine nanotechnology

Applicants:
Massachusetts Institute of Technology
President and Fellows of Harvard College
The Brigham and Women's Hospital, Inc.
The Children's Medical Center Corporation

Headword:
Nanocarriers/ MASSACHUSETTS INSTITUTE

Relevant legal provisions:
EPC Art. 76(1)

Keyword:
Divisional application - subject-matter extends beyond content of earlier application (yes)

Decisions cited:
G 0001/05

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 2290/15 - 3.3.04

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

Appellant: (Applicant 1)	Massachusetts Institute of Technology 77 Massachusetts Avenue Cambridge, MA 02139 (US)
Appellant: (Applicant 2)	President and Fellows of Harvard College 17 Quincy Street Cambridge, MA 02138 (US)
Appellant: (Applicant 3)	The Brigham and Women's Hospital, Inc. 75 Francis Street Boston, MA 02115 (US)
Appellant: (Applicant 4)	The Children's Medical Center Corporation 55 Shattuck Street Boston, Massachusetts 02115 (US)
Representative:	Potter Clarkson The Belgrave Centre Talbot Street Nottingham NG1 5GG (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 16 July 2015 refusing European patent application No. 11075205.2 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	D. Luis Alves
	L. Bühler

Summary of Facts and Submissions

I. The applicants (appellant) filed an appeal against the decision of the examining division refusing the European patent application No. 11 075 205.2 (hereinafter "the application"), entitled "*Vaccine nanotechnology*". The application was filed as a divisional application of the European patent application No. 08 839 738.5, which was filed as an international patent application and published as WO 2009/051837 (hereinafter the "earlier application as filed" or the "earlier application").

II. The decision under appeal dealt with a main request and 11 auxiliary requests. The examining division held that the subject-matter of the claims according to the main request and auxiliary request 1 did not involve an inventive step (Article 56 EPC). The subject-matter of the claims according to each of auxiliary requests 2 to 11 extended beyond the content of the application and that of the earlier application as filed (Articles 123(2) and 76(1) EPC).

III. With the statement of grounds of appeal the appellant filed 13 sets of claims as the main request and auxiliary requests 1 to 12. The appellant requested that the decision under appeal be set aside and, on an auxiliary basis, that oral proceedings be held.

IV. The board appointed oral proceedings and subsequently issued a communication pursuant to Article 15(1) RPBA indicating its preliminary opinion with respect to Article 56 EPC.

Additionally, with reference to decision G 10/93, the board informed the appellant that in its preliminary

opinion none of the claim requests on file complied with the requirements of Articles 76(1) and 123(2) EPC.

V. In reply to the summons the appellant filed two sets of claims as auxiliary requests 1 and 2 to replace all sets then on file as auxiliary requests.

In reply to the board's communication, by a letter of 13 November 2018, the appellant replaced the previous claim requests with sets of claims of a main request and an auxiliary request 1.

VI. Claim 1 of the main request reads as follows:

"1. Solid polymeric nanocarriers having a mean geometric diameter of between 60 nm and 250 nm, wherein the nanocarriers comprise a T cell peptide antigen, and a dendritic cell immunostimulatory agent selected from the group consisting of: toll-like receptor agonists; CD40 agonists; and agents which promote dendritic cell maturation; and wherein one or more of the T cell antigen and the immunostimulatory agent is covalently bound to the nanocarriers or to a polymer from which the nanocarriers are made."

Claim 1 of auxiliary request 1 reads as claim 1 of the main request, except for the list of dendritic cell immunostimulatory agents. Thus, the claim reads as follows:

"1. ... [as in claim 1 of the main request] ... a dendritic cell immunostimulatory agent selected from the group consisting of: toll-like receptor agonists; CD40 agonists; agents which promote dendritic cell maturation; cytokines; proinflammatory stimuli released from necrotic cells; and activated components of the

complement cascade; ... [as in claim 1 of the main request]."

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

Main request - Article 76(1) EPC

Each of the features as disclosed in the description of the earlier application was applicable and combinable with all aspects of the invention because none of them was disclosed in a specific context. Thus, the features in claim 1 had not been combined from separate contexts. In this respect reference was made to the Case Law of the Boards of Appeal of the EPO, 8th edition, 2016, on page 419, point 1.4.1.

Moreover, the earlier application was to be read as a whole.

In this respect the importance of nanocarrier size was clear from both paragraph 18 and the fact that mimicking virus particles was the essence of the invention, as could be recognised from paragraphs 196 and 198, as well as from Figure 1, which illustrated carrier arrival at the target location and take up by macrophages. The size ranges in paragraph 18 were consistent with this concept of the invention. Each size range was equally suitable as each had 60 nm as the preferred lower limit and all upper limits were within 500 nm and thus within virus size.

Furthermore, the examples in the application built on each other, leading the skilled person to impart preferences on the general disclosure. Reference was

made to example 1, paragraph 538, using a particle size of 200 nm; example 3, using particles of about 100 nm, as seen from paragraph 150, and having covalently bound Fc; and finally example 5, disclosing a solid polymeric particle having, covalently bound to it, a T cell antigen and a dendritic cell immunostimulatory agent. In conclusion, taken together the examples provided the teaching that the important features of the nanocarrier were the size and covalent bond. Likewise, the solid and polymeric nature of the nanocarrier were features derivable from the examples as a whole.

Finally, the skilled person would also arrive at the combination of features now claimed by reading the following passages of the earlier application in order: paragraph 8, 10, 11 12, 22, 67, 105, 196, 197, 198 and finally paragraph 200.

Claim 1 indicated three specific dendritic cell immunostimulatory agents, whereas the earlier application disclosed a longer list of such agents. However, deleting some members of the list did not give rise to any new information in the present situation. In this context reference was made to decisions T 615/95 and T 1506/13.

Auxiliary request - Article 76(1) EPC

The list of immunostimulatory agents in claim 1 was the same as in paragraph 67 of the description. Therefore, any objection based on a limitation of claim 1 to three classes of the immunostimulatory agent in combination with the other features of the claim no longer applied. No selection had been made from within the list in paragraph 67.

VIII. Oral proceedings took place as scheduled and at their end the chair announced the board's decision.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claim requests as filed with the letter dated 13 November 2018.

Reasons for the Decision

Main request - Article 76(1) EPC

1. Article 76(1) EPC determines that a European divisional application may be filed only in respect of subject-matter which does not extend beyond the content of the earlier application as filed.

The "content" within the meaning of Article 76(1) EPC is what the skilled person would directly and unambiguously derive from the whole of the earlier application as filed (see G 1/05, point 9.2 of the Reasons). If an amendment exceeds these limits, the requirements of Article 76(1) EPC are not fulfilled.

Content of the earlier application as filed

2. Although not mentioned by the appellant in their arguments, the board considers it noteworthy that the earlier application contains 386 claims, of which claims 225 to 360 and 369 to 386 are directed to nanocarriers *per se*.

3. The description of the earlier application consists of 165 pages subdivided into 573 paragraphs. It introduces the invention on page 2 in paragraph 6 as follows:

"*The present invention provides synthetic nanocarriers for modulating the immune system. The synthetic nanocarriers comprise one or more of an immunomodulatory agent, an immunostimulatory agent, and a targeting agent (also referred to herein as "targeting moiety"). The immunomodulatory agent induces an immune response in B and/or T cells.*".

Thus, in this paragraph the earlier application foresees that the nanocarriers may comprise one or more of the following three agents: (i) an immunomodulatory agent; (ii) an immunostimulatory agent; and (iii) a targeting agent.

The disclosure in the subsequent paragraphs may be illustrated as follows. Paragraph 7 discloses the therapeutic uses of the nanocarriers. Paragraphs 8 to 22, present the skilled person with multiple parameters which can be used to define the nanocarriers.

Paragraph 8 lists ways in which the agent is bound to the nanocarrier, which include covalent binding and non-covalent binding, the latter of which is further defined as ionic bonding, hydrophobic bonding or physical entrapment.

Paragraph 9 concerns the administration of nanocarriers in the case of allergen exposure.

Paragraph 10 discloses that the nanocarrier may be bound to one or more of the agents (i) an immunomodulatory agent; (ii) an immunostimulatory

agent; and (iii) a targeting agent. The remainder of the paragraph then discloses compositions comprising mixtures of these nanocarriers, which may all be identical or may differ from each other, on account of either the agents they carry or otherwise. In these compositions each nanocarrier may carry one or more of the agents (i) to (iii).

Paragraph 11 refers to nanocarriers being used to "*mimic* [...] *what the immune system 'sees' when exposed to antigen*".

Paragraph 12 states further parameters which may characterise the nanocarriers, as follows: "*One important aspect is that the nanocarriers can be controlled in terms of size, density of agent, degree and location of targeting, degradation, release of agent, etc.*".

In paragraph 13 the skilled person is presented with possible chemical "*scaffolds*" of the nanocarrier: it can be *"composed of polymer and/or non-polymer*", *"protein-based, nucleic acid-based, carbohydrate-based*", "*composed of crosslinking chains of molecules*", or alternatively may be formed of a number of nanoparticles, which in turn may for example be lipid-based, polymeric, metallic, surfactant-based emulsions or dendrimers.

Paragraph 14 presents a list of polymers in cases where the scaffold is a polymer.

Paragraphs 15 and 16 then describe the preparation of the nanocarrier by self-assembly, in particular by using amphiphilic materials, and the resulting nanocarriers.

Paragraph 17 discusses how the charge of the nanocarrier may be varied, in particular the charged moieties at its surface.

Paragraph 18 discloses a number of nanocarrier size ranges.

Paragraph 19 presents nanocarriers comprising possible combinations of the agents (i) an immunomodulatory agent; (ii) an immunostimulatory agent; and (iii) a targeting agent.

Paragraph 20 is dedicated to nanocarriers carrying B cell antigens, such as allergens as disclosed in paragraph 21.

Paragraph 22 discloses nanocarriers in which an immunomodulatory agent (i) is present and is a T cell antigen. A combination with a targeting agent (iii) is foreseen. The T cell antigen may be carried on the surface of the nanocarrier and/or encapsulated within it.

In summary, upon reading through paragraphs 6 to 22 of the description, the skilled person is presented with a number of parameters by which the nanocarriers can be defined. These include: size; density of agent; degree and location of targeting; degradation; release of agent; whether each nanocarrier provides one or more of the agents (i) an immunomodulatory agent, (ii) an immunostimulatory agent, and (iii) a targeting agent; whether those agents are provided as mixtures of nanocarriers where a single nanocarrier combines several agents or each agent is provided in a separate nanocarrier, said nanocarriers being otherwise identical to or different from each other; the chemical

"scaffold" of the nanocarrier in terms of polymer/ lipid/metallic composition and surface charge; means of carrying the agents such as covalent or non-covalent binding.

Paragraphs 6 to 22, in particular paragraphs 19 and 22, do not disclose the combination (i) and (ii).

The remainder of the description presents further possible parameters by which the nanocarriers can be defined.

These include, in paragraph 101, the morphology of the nanocarrier as well as its inner structure, i.e. whether it is solid or hollow and whether it comprises one or more layers surrounding a core. This paragraph is also the first instance in the description of the earlier application that refers to a solid structure of the nanocarriers.

Basis for the combination of features according to claim 1

4. Claim 1 of the main request is directed to nanocarriers comprising the following combination of features (a) to (f):

(a) solid

(b) polymeric

(c) mean geometric diameter of between 60 nm and 250 nm

(d) presence of a T cell peptide antigen

(e) presence of a dendritic cell immunostimulatory agent selected from three classes of agents

(f) covalent binding of (d) and/or (e) to the nanocarrier or to the polymer from which the nanocarriers are made.

5. Given the disclosure in the earlier application as outlined above, in order to arrive at the combination of features in claim 1 the skilled person must bring together the following disclosures in the earlier application:

select from the three groups of agents disclosed in "Summary of the Invention" (see above) - (i) the immunomodulatory agent and (ii) the immunostimulatory agent - with (i) specifically being a T cell antigen and (ii) specifically consisting of three classes of dendritic cell immunostimulatory agents;

select the following parameters amongst all of the parameters disclosed in the application to characterise the nanocarrier: (a) inner structure; (b) chemical nature of the "scaffold"; (c) size; and (f) means of carrying the agent;

further select that (a) and (b) are specifically "solid" and "polymer"; that parameter (c) specifically is in the range of 60 to 250 nm in terms of mean average diameter; that parameter (f) specifically is covalent binding.

The appellant provided three main lines of reasoning as to why the skilled person would derive these selections

and their combination clearly and unambiguously from the earlier application.

Combining features disclosed in the description

6. In a first line of reasoning the appellant argued that each of the features as disclosed in the description was applicable and combinable with all aspects of the invention. Thus, the features recited in claim 1, which were all disclosed in the description, could not be considered to have been combined from separate contexts.

In the board's view, this argument amounts to a combinatorial approach whereby any conceptually possible combination of features disclosed in a document is considered to be actually disclosed. This approach, however, is not in accordance with the established jurisprudence of the boards of appeal when it comes to the determination of the disclosure content of a document. Rather, the boards have held that an application (or generally a document) must not be considered to be a "reservoir" from which features that the skilled person would understand as being separate in the absence of any indication to the contrary, can be combined to create a particular embodiment. Such an embodiment is not considered to emerge clearly and unambiguously from the content of the document(see Case Law of the Boards of Appeal of the EPO, 8th edition, 2016, II.E.1.4.1.).

Disclosure in the examples

7. In a second line of reasoning the appellant submitted that the application is to be read as a whole, and that in so doing the skilled person would construe the examples as disclosing preferred parameters for defining the nanocarriers and would impart those preferences on the general disclosure. Thus, the skilled person would derive the claimed subject-matter from the earlier application. In this context the appellant referred to examples 1, 3 and 5.

8. The board concurs with the appellant that in certain circumstances the skilled person may infer from the disclosure in examples that features are preferred in the context of an invention and that in turn, depending on the circumstances, it may be possible to combine those with the general description so as to arrive at a disclosure of claimed subject-matter (see Case Law of the Boards of Appeal of the EPO, 8th edition, 2016, II.E.1.3.2).

9. In the light of the appellant's argument, the question considered first will be whether in the present case the skilled person would derive from the examples preferences for certain parameters, whether general or specific, by which to characterise the claimed nanocarriers.

9.1 Example 1, starting at paragraph 518, concerns experiments addressing how viruses are cleared from lymph and how they are presented to B cells.
The appellant referred to paragraph 538, for mentioning a particle size of 200 nm; this paragraph of example 1 states " [...] *indicating that macrophages act as guardians against many structurally distinct pathogens.*

In contrast, virus-sized latex beads (200 nm) were poorly retained in the SCS after footpad injection (Figure 14E). Thus, SCS macrophages discriminate between lymph-borne viruses and other particles of similar size. ".

Hence, this passage discloses that particles - which are not nanocarriers - of a diameter of 200 nm were **not** recognised by macrophages as if they were a virus, i.e. the passage does not convey that 200 nm is a preferred particle size for the nanocarriers of the invention.

9.2 The appellant did not refer to example 2, entitled *"Exemplary Lipid-Based Vaccine Nanotechnology Architectures*", which discloses several conceptual nanocarrier architectures within the following three variants: liposome nanocarriers, liposome-polymer nanocarriers and lipid-stabilised polymeric nanocarriers (see also the corresponding Figures 3 to 10). All the possibilities in those figures are illustrated as comprising two immunomodulatory agents.

Thus, this passage focuses on lipid-based nanocarriers some of which may have a polymeric core.

9.3 Example 3 is entitled "*In vivo targeting of SCS-Mph using Fc fragments from human IgG*". Accordingly, nanocarriers which comprise a targeting moiety, i.e. an agent contemplated in the "Summary of the Invention", in this case Fc, are used in this example. As reasoned by the appellant, the characteristics of the nanocarriers used in this example are disclosed in a different part of the description
- paragraph 150 - which refers to PEG (poly ethylene glycol)-PLGA (polylactic acid-co-glycolic acid) nanocarriers having a diameter of approximately 100 nm.

This example discloses the use of a specific solid, polymeric nanocarrier, having a diameter falling within the range of claim 1 but, in relation to nanocarriers comprising a targeting moiety, which is not an alternative referred to in claim 1.

9.4 Example 4 also concerns targeted nanoparticles. The example states that PLGA nanoparticles are used but makes no mention of their size, which, in contrast to example 3, cannot be inferred from other parts of the description either.

9.5 Example 5 shows the results of experiments with nanocarriers comprising a T cell peptide antigen (i) and a toll-like receptor agonist (ii). Two embodiments of nanocarriers are used, both carrying encapsulated agent (i). Agent (ii) is provided in two different ways: in one embodiment it is encapsulated whereas in the other embodiment it is covalently bound to the polymer.

Example 5 discloses a solid nanocarrier, of the same polymer as used in examples 3 and 4, but fails to disclose its size and that both agents (i) and (ii) are covalently bound.

9.6 To sum up, in relation to the question of whether or not the skilled person would derive from the examples preferences for certain parameters, whether general or specific, by which to characterise the claimed nanocarriers, the following is found: by disclosing a particle of a certain size which is not taken up by a macrophage, example 1 rather discloses the absence of a preference; example 2 discloses liposomes and lipid-stabilised polymeric nanocarriers, and thus does

not focus on the polymeric nature of the nanocarriers; examples 3 to 5 disclose solid, polymeric nanocarriers, yet neither example 3 nor example 4 is directed to a nanocarrier having the combination of an immunomodulatory agent (specifically: a T cell peptide antigen) and an immunostimulatory agent (specifically: a dendritic cell stimulatory agent), covalently bound, as required by claim 1. Example 5 discloses this combination as one of the embodiments, yet the two agents are not both covalently bound. Only example 3 discloses the nanocarrier size, yet it does so in the context of nanocarriers having a targeting moiety.

10. Thus, apart from pointing to solid (PLA/PLGA) polymeric nanocarriers, the board cannot infer from the examples preferences for parameters to characterise the nanocarriers.

11. Having arrived at this conclusion, there is no need to answer the question of whether imparting those preferences, if they existed, on the general description would result in the disclosure of the claimed invention.

12. The appellant also submitted that disclosure of the claimed nanocarrier could be arrived at by a generalisation of example 5 in the light of the description. The board is not persuaded by this argument. Example 5 is the only example illustrating a nanocarrier that is solid, a polymer, and comprises an immunomodulatory agent and a dendritic cell immunostimulatory agent, as required by claim 1, of which the immunostimulatory agent is covalently bound. For the further features (and their combination) the skilled person would have to find direct and unambiguous disclosure in the application. However,

there is no such direct and unambiguous disclosure for the particular features. The following references illustrate that the skilled person would not derive from the description a preference for either the type of binding, i.e. covalent, or the size range referred to in claim 1.

With regard to the type of binding, the application discloses in paragraph 104:

"*[00104] In some embodiments, an immunomodulatory agent, targeting moiety, and/or immunostimulatory agent can be covalently associated with a nanocarrier. In some embodiments, covalent association is mediated by a linker. In some embodiments, an immunomodulatory agent, targeting moiety, and/or immunostimulatory agent is non-covalently associated with a nanocarrier. For example, in some embodiments, an immunomodulatory agent, targeting moiety, and/or immunostimulatory agent is encapsulated within, surrounded by, and/or dispersed throughout a polymeric matrix, a lipid membrane, etc. Alternatively or additionally, an immunomodulatory agent, targeting moiety, and/or immunostimulatory agent may be associated with a polymeric matrix, a lipid membrane, etc. by hydrophobic interactions, charge interactions, van der Waals forces, etc.*"

With regard to possible size ranges for the carriers, the application discloses in paragraph 18:

"*[0018]* [...] *In some embodiments, the mean geometric diameter is between 100-400 nm, 100-300 nm, 100-250 nm, or 100-200 nm. In some embodiments, the mean geometric diameter is between 60-400 nm, 60-350 nm, 60-300 nm, 60-250 nm, or 60-200 nm. In some embodiments, the mean geometric diameter is between 75-250 nm.*"

13. The skilled person could not derive a preference for the size range in claim 1 from paragraphs 196 and 198 in combination with Figure 1 either. Paragraph 196 and Figure 1 do not indicate any size for the nanocarriers. As to paragraph 198, it both refers to viral particles "*that measure tens to hundreds of nanometers in diameter*" and discloses specific nanocarriers consisting of PLGA particles surface-stabilised with lipid and PEG in a size range of 50 to 150 nm. Thus, the specific size range, which differs from the size range in claim 1, is disclosed for a specific nanocarrier composition.

Reading selected parts of the description

14. Finally, further developing their second argument, the appellant reasoned that the skilled person would arrive at the combination of features now claimed by reading the application as follows: paragraph 8, disclosing covalent binding; paragraph 10, disclosing bound "agents"; paragraph 11, second sentence, disclosing the concept of "mimicking"; paragraph 12, second sentence, disclosing that nanocarriers can be controlled in terms of size; paragraph 22, disclosing that the T cell antigen may be covalently associated; paragraph 67, disclosing the three DC stimulatory agents in the claim; paragraph 105, referring to a wide variety of polymers and thus disclosing the feature "polymer"; paragraph 196, last sentence, referring to the concept of virus mimicking; paragraph 197, last sentence, referring to Figure 1; paragraph 198 disclosing a size of tens to hundreds of nanometres and the polymeric nature of the nanoparticles, thus linking the concepts

of size and polymer; paragraph 200, disclosing polymeric nanoparticles.

15. In the board's view, the essence of this proposed reading of the application is to direct the reader to selected parts of the application whilst intervening parts are ignored. This, however, does not correspond to what the reader is presented with when reading the document as a whole. The suggested sequential reading of paragraphs 8, 10, 11 and 22, for example, ignores the intervening paragraphs, which provide further parameters and multiple alternatives for each parameter, all of which would have been presented to the skilled person as being equally applicable.

Moreover, there is nothing pointing the skilled person to read only the selected paragraphs and only selected parts of them.

16. In view of the observations in points 1 to 15 above, the board thus comes to the conclusion that the subject-matter characterised by the combination of features in claim 1 extends beyond the content of the earlier application as filed, contravening the requirements of Article 76(1) EPC.

Auxiliary request 1 - Article 76(1) EPC

17. Claim 1 of this request differs from claim 1 of the main request on account of the number of members of the group from which the dendritic cell immunostimulatory agents are selected.

18. However, the board's conclusion with respect to the main request is not based on the specific members

forming the list of dendritic cell immunostimulatory agents. Thus, modifying the list is immaterial to the above reasoning with respect to the main request, which remains applicable to the present request.

19. In conclusion, the subject-matter of claim 1 of auxiliary request 1 does not comply with the requirements of Article 76(1) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

S. Lichtenvort G. Alt

Decision electronically authenticated