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Datasheet for the decision of 19 October 2016

Case Number: T 0346/12 - 3.3.04

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Language of the proceedings: EN

Title of invention:
Methods of modulating an immune response using immunostimulatory sequences and compositions for use therein

Patent Proprietor:
Dynavax Technologies Corporation

Opponents:
Pfizer Vaccines LLC (Opponent 1)
Cytos Biotechnology AG (Opponent 2)

Headword:
Immunostimulatory sequences/DYNAVAX

Relevant legal provisions:
EPC Art. 54(2)

Keyword:
Novelty - (no) - main and auxiliary requests 1 to 8

Decisions cited:

Catchword:

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Case Number: T 0346/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 19 October 2016

Appellant I: (Patent Proprietor)	Dynavax Technologies Corporation 2929 Seventh Street, Suite 100 Berkeley, CA 94710 (US)
Representative:	Roques, Sarah Elizabeth J A Kemp 14 South Square Gray's Inn London WC1R 5JJ (GB)
Appellant II: (Opponent 1)	Pfizer Vaccines LLC 235 East 42nd Street New York NY 10017-5755 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Respondent: (Opponent 2)	Cytos Biotechnology AG Wagistrasse 25 8952 Schlieren (CH)
Representative:	Wichmann, Hendrik Wuesthoff & Wuesthoff Patentanwälte PartG mbB Schweigerstraße 2 81541 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 15 December 2011 concerning maintenance of the European Patent No. 1204425 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	A. Chakravarty
	M. Blasi

Summary of Facts and Submissions

I. European patent No. EP-B-1 204 425, entitled "*Methods of modulating an immune response using immuno-stimulatory sequences and compositions for use therein*" was granted with 13 claims. The patent was opposed by two parties on the grounds of lack of novelty and inventive step (Article 100(a) EPC), failure to provide a disclosure of the invention sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC) and because the subject-matter of the European patent extended beyond the content of the application as filed (Article 100(c) EPC).

II. Both the patent proprietor (appellant I) and opponent 1 (appellant II), filed appeals against the interlocutory decision of the opposition division that the patent could be maintained in amended form (Article 101(3)(a) EPC). Opponent 2 is party as of right to the appeal proceedings (respondent).

III. The opposition division considered a main and three auxiliary requests. It held that the subject-matter of claims 1 and 11 of the main request lacked novelty with respect to the disclosure of documents WO 98/16247 (D2) and Klinman D. et al, Vaccine, Vol. 17, 1999, 19-25 (D3). The subject-matter of claim 1 of auxiliary requests 1 and 2 lacked novelty for the same reasons as did that of claim 1 of the main request. The subject-matter of auxiliary request 3 was held to meet the requirements of the EPC.

IV. With the statement of grounds of appeal, appellant I requested that the patent be maintained in amended form on the basis of the claims of the main or auxiliary

requests 1 or 2, all filed before the opposition division on 9 June 2011 or on the basis of auxiliary request 3, filed at the oral proceedings before the opposition division on 17 June 2011. With the reply to the statement of grounds of appeal of appellant II, appellant I submitted further sets of claims as auxiliary requests 4 to 8.

V. Independent claims 1 and 11 of the main request are as follows:

"1. Use of an immunomodulatory polynucleotide comprising an immunostimulatory sequence (ISS) and a first antigen in the manufacture of a medicament for stimulating a Thl immune response to a second antigen in an individual, wherein the polynucleotide and first antigen are (a) proximately associated by conjugation, encapsulation, adsorption onto a surface or linkage to a platform molecule and (b) administered in an amount sufficient to stimulate an immune response to the second antigen upon exposure to the second antigen, wherein the second antigen is administered at:

(i) exactly the same time as the first antigen; and

(ii) the same site or location as the first antigen.

11. A composition comprising an immunomodulatory polynucleotide comprising an ISS proximately associated with a first antigen and further comprising a second antigen, wherein the ISS is proximately associated with the first antigen by conjugation, encapsulation, adsorption onto a surface or linkage to a platform molecule".

Claim 1 of auxiliary requests 1 and 2 is identical to claim 1 of the main request.

Claim 11 of auxiliary requests 5, 6 and 7 further defines the antigens, *inter alia*, as follows - "*wherein:... the first antigen is an allergen and the second antigen is another allergen* [...]".

Claim 11 of auxiliary request 3 further defines the second antigen as follows - "*wherein the second antigen is not proximately associated with the polynucleotide and the first antigen*".

Claim 11 of auxiliary request 4 further defines the second antigen as follows - "*wherein the second antigen is not proximately associated by conjugation, encapsulation, adsorption onto a surface or linkage to a platform molecule with the polynucleotide and the first antigen*".

Claim 11 of auxiliary request 8 is identical to claim 11 of the main request.

VI. In a communication pursuant to Article 15(1) RPBA, the board gave its preliminary and non—binding opinion on some of the substantive and legal issues concerning the appeal. It informed the parties that it was inclined to agree *inter alia* with the argument made by appellant II in the statement of grounds of appeal (section 4.3), that the subject-matter of claim 1 of auxiliary request 3 lacked novelty with respect to the disclosure on page 15 of WO 98/55495 (D1) of an immunostimulatory sequence (ISS) proximately associated with a first antigen further associated with an adjuvant, where the adjuvant itself may be a second antigen.

VII. Appellant I replied to the board's communication with a letter in which the points raised by the board were addressed.

VIII. All parties informed the board that they would not attend the oral proceedings. The requests for oral proceedings were withdrawn.

IX. Oral proceedings before the board were held on 19 October 2016, in the absence of the parties. At the end of these proceedings the Chairwoman announced the decision of the board.

X. Appellant I's written submissions relevant to the decision can be summarised as follows:

Novelty - Article 54 EPC

Main request and auxiliary requests 1 and 2

The subject-matter of claims 1 and 11 of the main request was limited to embodiments in which the first antigen but not the second antigen was proximately associated with the immunomodulatory polynucleotide comprising an ISS. This view was supported by the examples of the application as filed, which described only experiments in which a first antigen was proximately associated with an ISS-containing polynucleotide, but a second antigen was not proximately associated with the ISS-containing polynucleotide or the first antigen.

It followed from the claim construction that the subject-matter of claims 1 and 11 was novel over the disclosure of both documents D2 and D3, which were concerned only with complexes where both the first and

second antigens were proximately associated with the ISS.

The subject matter of the claims of auxiliary requests 1 and 2 was novel for the reasons given for the main request.

Auxiliary request 3

The request corresponded to the claims allowed by the opposition division and should therefore be considered allowable. The disclaimer in claims 1 and 11 only made explicit a feature already present in the main request.

The composition of claim 11 was not directly and unambiguously derivable from the disclosure of document D1 because it required the reader to make an undisclosed selection from three separate lists as follows: firstly it was necessary to select that the ISS conjugated to an antigen and then to select use of the ISS-antigen conjugate together with an adjuvant. Finally, an antigenic adjuvant had to be selected from a list of adjuvants found at page 15 of D1. Furthermore, there was no pointer or preference to be found in the disclosure of document D1 that the now claimed selection was in any way preferred.

Auxiliary requests 4 to 8

The subject matter of auxiliary request 4 complied with the requirements of Article 54 EPC for the reasons discussed above for auxiliary request 3 and as discussed previously for the main request.

Auxiliary request 5 was identical to auxiliary request 1, except that claims 1 and 11 had been amended to explicitly specify that the second antigen was not proximately associated with the polynucleotide and the first antigen. Additionally, claim 11 specified a relationship between the first and second antigens which was not disclosed in document D1.

Auxiliary Request 6 was the same as auxiliary request 1, except that claims 1 and 11 were amended to specify that the first and second antigens were related in terms of source. Claim 1 also included the same particular combinations of first and second antigens as set out in claim 11.

Auxiliary request 7 was identical to auxiliary request 6, with the addition of the amendments made to arrive at auxiliary request 3. Its subject matter complied with the requirements of Article 54 EPC for the same reasons as auxiliary request 3 and the main request.

XI. Appellant II's written submissions relevant to the decision can be summarised as follows:

Novelty - Article 54 EPC

Auxiliary request 3

Claim 11 of this request was, *inter alia*, for a composition in which an immunomodulatory polynucleotide comprising an ISS was proximately associated with a first antigen and further comprising a second antigen. Only the first antigen needed to be proximately associated with the immunomodulatory polynucleotide.

Claim 30 of document D1 related to an immunomodulatory composition comprising an immmunomodulatory oligonucleotide comprising at least one immunostimulatory octanucleotide sequence, comprising an antigen and further comprising an adjuvant. Suitable adjuvants were defined on page 15, lines 19 to 25 and included for example Cholera toxin B subunit, a well known antigen. Claim 32 related to a composition according to claim 30 in which the antigen was conjugated to the immunomodulatory nucleotide.

Therefore, D1 disclosed a composition falling within the ambit of claim 11 in which an ISS is proximately associated with a first antigen by conjugation and which further comprises a second antigen not proximately associated with the ISS and the first antigen.

XII. Appellant I requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request, or alternatively, of auxiliary requests 1 or 2, all as filed with the statement of grounds of appeal, or further alternatively, that the appeal of appellant II be dismissed (i.e. the patent be maintained on the basis of the set of claims as considered allowable by the opposition division), or further alternatively, whilst setting aside the decision under appeal, that the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 4 to 8 as filed together with the reply to the statement of grounds of appellant II.

XIII. Appellant II requested that the appeal of appellant I be dismissed, that the decision under appeal be set aside and the patent be revoked.

XIV. The respondent did not make any substantive submissions in these appeal proceedings.

Reasons for the Decision

Procedural issues

1. Despite the fact that all requests for oral proceedings had been withdrawn, the board considered it expedient to hold oral proceedings as scheduled, in accordance with Article 116(1) EPC. The appeal proceedings were thus continued in the absence of the duly summoned parties, pursuant to Rule 115(2) EPC. The parties were treated as relying on their written cases. (Article 15(3) RPBA).

Novelty - Article 54 EPC

Main request and auxiliary requests 1 and 2

Claim 1

2. Claim 1 is for the use of an immunomodulatory polynucleotide comprising an immunostimulatory sequence (ISS) proximately associated with a first antigen by conjugation, for the therapeutic purpose of stimulating a Thl immune response to a second antigen in an individual. The second antigen is administered at (i) exactly the same time as the first antigen; and (ii) the same site or location as the first antigen.

3. The board considers that the skilled person reading the claim, would understand its subject-matter to include embodiments in which the second antigen is associated, proximally or otherwise, with the first antigen-ISS complex. As noted by appellant II, this view is

supported by paragraph [0081] of the description of the patent, which relates to just such an embodiment - "*A second antigen may be any antigen other than the first antigen, and can be* ***different antigenic regions from the same polypeptide***" (emphasis added by the board).

4. Document D3 discloses stable complexes between biotinylated, immunostimulatory CpG oligonucleotides (which qualify as an "*ISS*" as defined in the patent in suit), ovalbumin and biotinylated avidin (see page 22, right column). These complexes are administered to a subject and were found to be "*extremely immunogenic*" (*ibid*).

5. Both ovalbumin and avidin are proteins and may act as antigens. Thus, avidin may be regarded as the first antigen mentioned in the claim and ovalbumin as the second or *vice versa*. Since the ovalbumin-avidin-ISS complexes disclosed in document D3 comprise a first antigen and second antigen both conjugated to an ISS, their administration to a subject will automatically result in conditions (i) and (ii) of the claim being met.

6. The board therefore considers that the subject-matter of claim 1 of the main and auxiliary requests 1 and 2 request lacks novelty in the light of the disclosure of document D3.

Main request and auxiliary requests 3, 4 and 8

Claim 11

7. Claim 11 of the all of the above requests is for a composition comprising an ISS proximately associated

with a first antigen by conjugation and further comprising a second antigen.

Claim 11 of the main and eighth auxiliary request does not specify whether the second antigen is associated with the polynucleotide-first antigen complex.

Claim 11 of auxiliary request 3 specifies that the second antigen is not proximately associated with the polynucleotide-first antigen complex.

Claim 11 of auxiliary request 4 excludes the possibility that the second antigen is proximally associated with the polynucleotide-first antigen complex by conjugation, encapsulation or adsorption onto a surface but does not exclude its association with the polynucleotide-first antigen complex by other means.

Thus, the subject-matter claim 11 of the each of the main request and of auxiliary requests 3, 4 and 8 includes as an embodiment, a composition in which the second antigen is separate (i.e. not associated proximally or otherwise) from the polynucleotide-first antigen complex.

8. Document D1 discloses "*compositions which comprise an ISS-antigen conjugate [...] and an adjuvant*" (see claims 30 and 32 and page 8, lines 19 to 23). "*Suitable adjuvants*" are disclosed on page 15, where a list including several antigens, e.g. "*muramyl peptide, [...] mycobacterium cell wall preparations, [and] cholera toxin B subunit*" is to be found. The adjuvant and the immunogenic composition are administered together but are not "*proximately associated*". Thus document D1 discloses a composition falling within the

ambit of the claim by way of a combination of the subject-matter of claim 32 with an antigenic adjuvant chosen from the list on page 15.

9. In view of the above, the board is satisfied that the skilled person reading the document would find in it a direct and unambiguous disclosure of a composition that falls within the ambit of claim 1. The board therefore considers that the subject-matter of claim 11 of the main and auxiliary requests 3, 4 and 8 lacks novelty with respect to the disclosure of document D1.

10. Furthermore, the stable complexes between biotinylated CpG oligonucleotides (ISS), ovalbumin and biotinylated avidin disclosed in document D3 (points 5 and 6 above) constitute an embodiment of claim 11 of the main request and auxiliary request 8. The board therefore considers that the subject-matter of claim 11 of the main and auxiliary request 8 lacks novelty in the light of the disclosure of document D3.

Auxiliary requests 1, 5, 6 and 7

Claim 11

11. The subject-matter of claim 11 of all these requests includes, as an embodiment, a composition comprising an immunomodulatory polynucleotide comprising an ISS proximately associated with a first antigen by conjugation and further comprising a second antigen which is not proximately associated with the immunomodulatory polynucleotide and the first antigen complex and in which the first antigen is an allergen and the second antigen is another allergen.

12. The skilled person would recognise that the term allergen "*means an antigen or antigenic portion of a molecule, usually a protein, which elicits an allergic response upon exposure to a subject*" (see patent, paragraph [0037]). They would also recognise that, due to differences between individuals in their response to antigens, some antigens will be allergens for some individuals but not for others. It is for this reason that tests such as the "*wheal and flare test*" described in paragraph [0037], need to be carried out.

13. The board therefore holds that the skilled person would consider that any antigen has the potential to also be an allergen.

14. The subject-matter of claim 11 of auxiliary requests 1 and 5 to 7 thus lacks novelty with respect to the disclosure of document D1 for the same reasons as the subject-matter of claim 11 of the main request.

15. In summary, the subject-matter of claim 1 of the main request and of auxiliary requests 1 and 2 lacks novelty over the disclosure of document D3. The subject-matter of claim 11 of the main request and of auxiliary requests 3, 4 and 8 lacks novelty over the disclosure of document D1, with claim 11 of the main and auxiliary request 8 also lacking novelty over the disclosure of document D3. Finally, the subject-matter of claim 11 of auxiliary requests 1, 5, 6 and 7 lacks novelty over the disclosure of document D1. Thus, no claim request meets the requirements of the Article 54 EPC.

Order

For these reasons it is decided that:

1. The appeal of appellant I is dismissed.

2. The decision under appeal is set aside and the patent is revoked.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated