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Datasheet for the decision of 21 October 2010

Case Number: T 0491/08 - 3.3.04

Application Number: 01932792.3

Publication Number: 1278541

IPC: A61K 39/21

Language of the proceedings: EN

Title of invention:
Improved immunogenicity using a combination of DNA and vaccinia virus vector vaccines

Applicants:
THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by the SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, et al

Headword:
Improved immunogenicity/GOVERNMENT USA

Relevant legal provisions:
EPC Art. 83

Keyword:
"Sufficiency of disclosure - main request and auxiliary requests 1-4 (no)"

Decisions cited:
G 0005/83, G 0002/88, G 0006/88, T 0019/90, T 1001/01, T 0609/02, T 0063/06

Catchword:
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Case Number: T 0491/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 21 October 2010

Appellants: THE GOVERNMENT OF THE UNITED STATES OF AMERICA
as represented by the SECRETARY OF THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES, et al
Bethesda, MD 20892 (US)

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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 25 September 2007 refusing European patent application No. 01932792.3 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: M. Wieser
B. Claes

Summary of Facts and Submissions

I. The appeal was lodged by the Applicants (Appellants) against the decision of the Examining Division to refuse under Article 97(1) EPC 1973 the patent application EP 01 932 792.3 (published as WO 01/82 964), having the title: "Improved immunogenicity using a combination of DNA and vaccinia virus vector vaccines".

II. The Examining Division decided that the main request and auxiliary requests 1 to 4 did not meet the requirements of Articles 83 and 84 EPC and that the subject-matter of claim 1 of all these requests was not novel (Article 54 EPC) in the light of the disclosure in document (6). Moreover, they decided that the subject-matter of the claims of auxiliary request 7 (auxiliary requests 5 and 6 having been withdrawn) did not involve an inventive step (Article 56 EPC).

III. The Board expressed its preliminary opinion in a communication dated 11 June 2010.

Oral proceedings were held on 21 October 2010.

IV. The Appellants requested that the decision under appeal be set aside and a patent be granted on the basis of the main request or one of auxiliary requests 1 to 4, all filed with their letter of 25 January 2008.

These requests were identical to the main request and auxiliary requests 1 to 4 before the Examining Division.

V. Claim 1 of each of Appellants' main request and auxiliary requests 1 to 4 read as follows:

Main request

"Use of

(1) a nucleic acid vaccine and

(2) a recombinant NYVAC or ALVAC pox virus vaccine encoding one or more of the same antigens encoded by the nucleic acid vaccine

in the preparation of a first and second medicament respectively to potentiate a $CD8^+$ response to human immunodeficiency virus-1 (HIV-1) epitopes in a human, wherein the nucleic acid and recombinant pox virus vaccines are capable of entering the cells of the human and intracellularly producing HIV-specific peptides that are presented on the cell's MHC class I molecules in an amount sufficient to stimulate a $CD8^+$ response, and further, wherein administration of the first and second medicaments potentiates an immune response compared to administration of either the nucleic acid or the recombinant pox virus by itself."

Auxiliary request 1

"Use of

(1) a DNA encoding as antigens one or more HIV-specific peptides selected from structural and non-structural viral peptides

(2) a recombinant NYVAC or ALVAC vector encoding one or more of the same antigens encoded by the DNA

in the preparation of a first and second medicament respectively to potentiate a $CD8^+$ response to human immunodeficiency virus-1 (HIV-1) epitopes in a human, wherein the DNA and recombinant NYVAC or ALVAC vector are capable of entering the cells of the human and intracellularly producing HIV-specific peptides that are presented on the cell's MHC class I molecules in an amount sufficient to stimulate a $CD8^+$ response, and further, wherein administration of the first and second medicaments potentiates an immune response compared to administration of either the DNA or the recombinant NYVAC or ALVAC vector by itself."

Auxiliary request 2

"Use of

(1) a DNA encoding as antigens one or more HIV-specific peptides selected from structural and non-structural viral peptides, in the preparation of a first medicament,

(2) a recombinant NYVAC or ALVAC vector encoding one or more of the same antigens encoded by the DNA, in the preparation of a second medicament,

to potentiate a $CD8^+$ response to human immunodeficiency virus-1 (HIV-1) epitopes in a human by administering the first medicament before the second medicament, wherein the DNA and recombinant NYVAC or ALVAC vector are capable of entering the cells of the human and

intracellularly producing HIV-specific peptides that are presented on the cell's MHC class I molecules in an amount sufficient to stimulate a $CD8^+$ response, and further, wherein administration of the first and second medicaments potentiates an immune response compared to administration of either the DNA or the recombinant NYVAC or ALVAC vector by itself."

Auxiliary request 3

"Use of

(1) a DNA encoding as antigens one or more HIV-specific peptides selected from structural and non-structural viral peptides, in the preparation of a first medicament,

(2) a recombinant NYVAC vector encoding one or more of the same antigens encoded by the DNA, in the preparation of a second medicament,

to potentiate a $CD8^+$ response to human immunodeficiency virus-1 (HIV-1) epitopes in a human by administering the first medicament before the second medicament, wherein the DNA and recombinant NYVAC vector are capable of entering the cells of the human and intracellularly producing HIV-specific peptides that are presented on the cell's MHC class I molecules in an amount sufficient to stimulate a $CD8^+$ response, and further, wherein administration of the first and second medicaments potentiates an immune response compared to administration of either the DNA or the recombinant NYVAC vector by itself."

Auxiliary request 4

"Use of

(1) a DNA encoding as antigens at least *gag* and *env* peptides, in the preparation of a first medicament,

(2) a recombinant NYVAC vector encoding one or more of the same antigens encoded by the DNA, in the preparation of a second medicament,

to potentiate a $CD8^+$ response to human immunodeficiency virus-1 (HIV-1) epitopes in a human by administering the first medicament before the second medicament, wherein the DNA and recombinant NYVAC vector are capable of entering the cells of the human and intracellularly producing HIV-specific peptides that are presented on the cell's MHC class I molecules in an amount sufficient to stimulate a $CD8^+$ response, and further, wherein administration of the first and second medicaments potentiates an immune response compared to administration of either the DNA or the recombinant NYVAC vector by itself."

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

(1) Journal of Virology, vol.72, no.12, 1998, pages 10180 to 10188

(4) Journal of Virology, vol.73, no.9, 1999 pages 7524 to 7532

(5) Nature Medicine, vol.4, no.4, 1998, pages 397 to 402

(16) JEM, vol.205, no.1, 2008, pages 63 to 77

VII. The submissions made by the Appellants, as far as they are relevant to the present decision, may be summarised as follows:

Nucleic acid vaccines and pox virus vaccines encoding one or more of the same antigens encoded by the nucleic acid vaccine could be prepared by a skilled person without difficulties. The achievement of the desired technical effect, namely the potentiation of a $CD8^+$ response to the specific antigens, has been demonstrated in example 1 of the application for the macaque/SIV system, which is an acknowledged animal model for human/HIV system. Therefore, the teaching of the application was sufficient to enable a skilled person to produce the prime and boost vaccines for HIV according to claim 1 of the main request and to administer them to a patient.

The fact that no concrete data and results obtained in humans were presented in the application could not be interpreted as a lack of sufficiency of disclosure. The Examining Division was wrong to base their argument under Article 83 EPC on the disclosure in prior art documents and to doubt the plausibility of the claimed subject-matter. According to established case law of the Boards of Appeal (for instance decision T 1001/01 of 11 October 2007) the Applicants were not required to provide clinical data obtained in humans at the filing date of the application. Moreover, example 2 of the

present application already reported the administration of vaccines according to claim 1 to humans. Clinical data proving the usefulness of the disclosed vaccines and the successful treatment of humans were provided in post published document (16).

Neither the definition of the specific antigens encoded by the nucleic acid of the vaccines, nor of the specifically used pox virus vector, nor of the specific regimen of priming and boosting was required to fulfil the requirements of Article 83 EPC.

The Examining Division's objection under Article 83 EPC, namely that in the field of DNA-vaccination data collected with a given combination of parameters were specific and did not allow any extrapolation or inference concerning other combinations, was not based on serious doubts, substantiated by verifiable facts, as required by decision T 19/90 (OJ EPO 1990, 476), but merely on assumptions concerning the subjective plausibility of the invention.

It could not be expected that the vaccine of the present application achieved the desired biological effect in 100% of patients treated, as this was not achieved by any other vaccine known today.

Reasons for the decision

Sufficiency of disclosure - Article 83 EPC

Main request

1. Under the EPC 1973 a patent for a further medical application could, pursuant to case law established by decision G 5/83 (OJ EPO 1985, 64), be granted for a claim directed to the use of a substance or composition for the manufacture of a medicament for a specified therapeutic application ("Swiss-type claim").

2. Claim 1 of the main request, which like claim 1 of all other of Appellants' requests is drafted in the so-called Swiss-type format, relates to the use of a nucleic acid vaccine and of a recombinant NYVAC or ALVAC pox virus vaccine for the preparation of a first and second medicament respectively. The two vaccines which encode one or more of the same antigens potentiate the $CD8^+$ response to HIV-1 epitopes in a human.

3. The application (published as WO 01/82 964) contains two examples.

   Example 1 describes the administration of DNA priming vaccines in combination with NYVAC-$SIV_{gag\text{-}pol\text{-}env}$ to Rhesus macaques. The Board has no reason to doubt that the macaque/SIV system is an animal model for human/HIV. The study design included 24 animals which were divided into three groups. Group A was vaccinated with a non-recombinant NYVAC virus, group B was vaccinated with NYVAC-$SIV_{gag\text{-}pol\text{-}env}$ and the animals of group C were

vaccinated with DNA plasmids constructs expressing the gag and env proteins of SIV_{239}, followed by vaccination with NYVAC-$SIV_{gag-pol-env.}$ The exact inoculation protocol is shown in figure 1. Groups A and B received four vaccinations (at weeks 0, 4, 24 and 52), group C was primed with DNA-$SIV_{gag-env}$ in weeks 0, 4 and 12 and boosted with NYVAC-$SIV_{gag-pol-env}$ in weeks 24 and 52. The results are presented in figures 2 to 8 and discussed on pages 19 to 22. The animals of group C showed a ten-fold higher lymphoproliferative response to p27 Gag and Env than the group B animals, they responded to more SIV groups and the responses were higher and their virological outcome was ameliorated after challenge with pathological SIV.

4. Page 22, lines 5 to 6, at the end of example 1 reads:

"ALVAC-based vaccine are similarly analyzed demonstrating that they also potentiate the immune response when used in conjunction with DNA vaccines."

Example 2 mentions "a vaccine regimen of a DNA priming vaccine followed by inoculation with a vaccine such as NYVAC or ALVAC", for humans at risk for HIV infection or for HIV infected patients. The DNA priming vaccine, of which multiple inoculations are typically administered, is said to express the HIV-1 gag,pro,tat,nef,rev and env genes. The patient, subsequently, is injected with a vaccine comprising about 10^8 pfu of a recombinant pox virus, e.g. NYVAC, expressing HIV-1 gag,pro,tat,nef, rev and env epitopes. The combination of these two vaccines is said to provide "a protective immune response in uninfected

patients and a therapeutic effect in those individuals already infected with HIV-1".

5. The only experimental data disclosed in the application refer to the animal model used in example 1 with the specific study design described therein, i.e. use of defined antigens and of a specific viral vector and inoculation following a precisely defined administration protocol. The application discloses no data for any other animal model study with a different experimental design, nor for any test carried out with humans.

6. Where a therapeutic application is claimed in the form allowed by the Enlarged Board of Appeal in its decision G 5/83 (OJ EPO 1985, 64), i.e. in the form of the use of a substance or composition for the manufacture of a medicament for a defined therapeutic application, attaining the claimed therapeutic effect is a functional technical feature of the claim (see G 2/88 and G 6/88, OJ EPO 1990, 93 and 114, Headnote III and point 9 of the reasons). As a consequence, under Article 83 EPC, unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application.

Taking into account the intrinsic difficulties for a compound to be officially certified as a drug (many years of experimental tests and high developmental costs), the patent system does not require an absolute proof that the compound is approved as a drug before it may be claimed as such.

However, it is required that the patent application provides some information in the form of, for example, experimental tests, to the effect that the claimed compound, administered as stated in the claims, has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the **prior art** or demonstrated in the application per se. Once this evidence is available from the patent application, then **post-published evidence** may be taken into account, but only to back up the findings in the patent application in relation to the use of the ingredient as a pharmaceutical, and not in itself to establish sufficiency of disclosure (cf decision T 609/02 of 27 October 2004, point 9).

7. In the present case, the application provides experimental data concerning the results of one specific example only, namely the animal model of claim 1. The example is carried out by following a study design wherein the antigens, the viral vector and the inoculation protocol are clearly defined (see point 3 above). In contrast to this, the subject-matter of claim 1 of Appellants' main request refers to the use of two compounds for the preparation of a first and second vaccine medicament respectively, wherein neither the antigens encoded by said compounds ("one or more of the same antigens"), nor the viral vector ("a recombinant NYVAC or ALVAC pox virus") are defined as in example 1. No inoculation protocol is mentioned in claim 1.

8. Consequently, the patent application itself does provide any information that the generically described compounds according to claim 1, when administered to a

human by whatever inoculation protocol, have a direct effect on a metabolic mechanism specifically involved in HIV-1 infection.

Following the rationale of decision T 609/02 (supra) it has to be examined if such a mechanism, which could form an acceptable basis for generic claim 1, is known from the prior art.

9. Document (1) disclose studies with mice and macaques evaluating a consecutive immunization strategy involving priming with DNA and boosting with rFPV vaccines encoding common HIV-1 antigens. The exact study design, including construction of plasmids and recombinant poxviruses as well as immunization protocols, is given on pages 10181 to 10182 ("Materials and Methods").

Document (4) demonstrates the immunogenicity of prime-boost vaccination against retroviral antigens in rhesus macaques who were given consecutive inocula of DNA and modified vaccinia virus Ankara (MVA) encoding SIV_{gag} sequences as multiepitope constructs (see abstract). High levels of CTL's specific for the used epitope were elicited in the animals. The exact study design is indicated on pages 7525 to 7526).

Document (5) discloses that a particular sequence of subunit immunizations with pre-erythrocytic antigens of Plasmodium berghei, consisting of single dose priming with plasmid DNA followed by a single boost with recombinant MVA expressing the same antigen, induced unprecedented complete protection against P. berghei sporozite challenge in two strains of mice (abstract).

The study shows that the protection, among others, depends on the specific vaccinia virus strain used (see page 398, left column, third paragraph and table 2).

10. Thus, all these relevant prior art documents, referring to prime-boost vaccination using a nucleic acid vaccine and a recombinant viral vector conditions, disclose a defined study design including number and kind of used antigens, construction and nature of used DNA plasmids and recombinant viral vectors and the precise inoculation protocol. Nothing in their disclosure can be interpreted as permitting data obtained by studies with a defined experimental set-up to be extrapolated to other studies with different or generically defined parameters.

11. The Appellants argued that the disclosure in post published document (16) should be taken into account, showing that the therapeutic effect of claim 1, potentiation of a CD8+ response to HIV-1 in humans, is indeed achieved by the claimed vaccines.

Document (16), published almost eight years after the priority date of the present patent application, reports phase I trials evaluating the safety and immunogenicity of a prime-boost regimen comprising recombinant DNA and the poxvirus vector NYVAC, both expressing a common immunogen consisting of Env, Gag, Pol, and Nef polypeptide domain from HIV-1clade C isolate, CN54. 40 volunteers were randomized to receive DNA C or nothing on day 0 and at week 4, followed by NYVAC C at weeks 20 and 24. The primary immunogenicity endpoints were measured at weeks 26 and 28 by the

quantification of T cell responses (see abstract and "Study design" on page 65).

The Board notes that, not only does document (16) report trials following a defined and specific study design (definition of immunogens and vectors plus a precise inoculation protocol), but also that this study design differs considerably from the study design of the animal model trial in example 1 and the, rather hypothetical, experiment in example 2 of the patent application.

According to decision T 609/02 (supra), the disclosure in post-published document (16) might only be taken into account for the question of sufficiency of disclosure if it was used to backup the findings in the patent application and not to establish sufficiency of disclosure on its own (see point (6) above). However, document (16), just like the disclosure in the patent application per se, does not allow any conclusion to be drawn on the medical applicability of the vaccines according to claim 1, which are only generically described and for which no inoculation protocol is indicated.

12. The Board holds that a presumption exists that, in general, a patent application relates to an invention which is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The weight of arguments and evidence required to rebut this presumption depends on its strength. A strong presumption requires more substantial arguments and evidence than a weak one. If, as in the present case, a patent application does not

contain detailed information of how to put the invention into practice; this requires less substantial arguments and evidence. Serious doubts whether the skilled person can carry out the invention as claimed, e.g. in the form of comprehensible and plausible arguments, are sufficient (see for instance decision T 63/06 of 24 June 2008, point 3.3.1).

In the light of the disclosure of the present application and considering the disclosure in the prior art and in post-published documents, the Board does not agree that the objection under Article 83 EPC, lack of sufficient disclosure, is based on hypothetical plausibility considerations only and not, as required by decision T 19/90 (supra), on serious doubts, substantiated by verifiable facts.

As a consequence, the Board decides that the application does not disclose the invention according to claim 1 of the main request in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, as required by Article 83 EPC.

Auxiliary request 1 to 4

13. Claim 1 of each of these requests contains amendments with regard to claim 1 of the main request.

Claim 1 of auxiliary request 1 defines "the nucleic acid vaccine" as being "a DNA encoding as antigens one or more HIV-specific peptides selected from structural and non-structural viral peptides".

Claim 1 of auxiliary request 2 additionally requires that the first medicament, containing the DNA, is administered before the second medicament, containing a recombinant NYVAC or ALVAC vector.

Claim 1 of auxiliary request 3 is additionally restricted to a recombinant NYVAC virus (reference to ALVAC virus has been deleted).

Finally, in claim 1 of auxiliary request 4, the antigens encoded by the DNA of the first medicament are defined as being "at least gag and env peptides", while the recombinant NYVAC vector is only defined by "encoding one or more of the same antigens encoded by the DNA".

14. Although these amendments all contribute to a more precise definition of the claimed subject-matter, none of the claims of the auxiliary requests is able to overcome the objection under Article 83 EPC raised and substantiated in points (1) to (12) above with regard to claim 1 of the main request.

None of the claims sufficiently defines the common immunogen expressed in the DNA priming vaccine and in the poxvirus vector boosting vaccine. Claim 1 of auxiliary requests 1 and 2, in addition, refer to the use of a vector (ALVAC) for which no experimental data at all exist. None of the claims indicates any inoculation protocol.

Finally, none of the claims mirrors the experimental set up underlying either the animal model tested in example 1, or the hypothetical example 2 of the

application, or the clinical trial disclosed in post-published document (16).

15. Therefore, the application also does not disclose the invention according to claim 1 of any of auxiliary requests 1 to 4 in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, as required by Article 83 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith