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Datasheet for the decision of 25 November 2008

Case Number: T 0534/07 - 3.3.08

Application Number: 98928434.4

Publication Number: 0979284

IPC: C12N 15/30

Language of the proceedings: EN

Title of invention:
Reagents for vaccination which generate a CD8 T cell immune response

Patentee:
Oxxon Therapeutics Limited

Opponents:
Sanofi Pasteur
OXFORD BIOMEDICA (UK) LTD.
Therion Biologics Corporation
POWDERJECT VACCINES INC.
Danisco US Inc

Headword:
CD8 T cells/OXXON THERAPEUTICS

Relevant legal provisions:
EPC Art. 134(5), 54, 56, 83

Relevant legal provisions (EPC 1973):
EPC Art. 108, 54(3)
EPC R. 65(1)

Keyword:
"Admissibility of appellant II's appeal - (no) - missing statement of grounds"
"Admissibility of appellant I's appeal - (yes)"
"Exclusion of representatives - (no) - no legal basis"
"Novelty - (yes)"
"Inventive step - (yes)"
"Sufficiency of disclosure (yes)"

Decisions cited:
J 0010/07, T 0606/89, T 0254/93, T 1009/97, T 0836/01, T 0315/03, T 0509/04

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0534/07 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 25 November 2008

Appellant I: (Patent Proprietor)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 31 January 2007 concerning maintenance of European patent No. 0979284 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
B. Günzel

Summary of Facts and Submissions

I. European patent No 0 979 284 with the title: "Reagents for vaccination which generate a CD8 T cell immune response" was granted with 45 claims on the basis of the European application No. 98928434.4 corresponding to the international application No. PCT/GB98/01681 published as WO 98/056919.

II. Seven oppositions were filed for lack of novelty and inventive step (Article 100(a) EPC) as well as lack of sufficiency of disclosure (Article 100(b) EPC). Opponents 1 and 7 subsequently withdrew their oppositions. The opposition division maintained the patent on the basis of the second auxiliary request filed at oral proceedings.

III. Appellants I (patentee), II and III (opponents 5 and 6) filed appeals. Appellants I and III submitted statements of grounds of appeal. That of appellant I was accompanied by a main request and six auxiliary requests. Appellant II did not submit a statement of grounds of appeal.

IV. Appellants I and III filed further submissions in answer to their respective appeals.

V. The board sent a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), indicating its preliminary, non-binding opinion.

VI. On 24 October 2008, appellant I sent a further submission in answer to the board's communication. The main request filed with the grounds of appeal was

withdrawn and replaced by the first auxiliary request in amended form - identified as "First Auxiliary Request- amended". Auxiliary requests 2 to 6 were to be renumbered as auxiliary requests 1 to 5 and two further auxiliary requests were enclosed.

Claim 1 of the main request (amended first auxiliary request) read as follows:

"1. Use of
(i) a priming composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, wherein the source of CD8+ T cell epitopes is a non-viral vector or a non-replicating or replication impaired viral vector, together with a pharmaceutically acceptable carrier; and
(ii) a boosting composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, including at least one CD8+ T cell epitope which is the same as a CD8+ T cell epitope of the priming composition, wherein the source of CD8+ T cell epitopes is a non-replicating or replication impaired recombinant poxvirus vector, together with a pharmaceutically acceptable carrier;
for the production of a vaccination kit against a disease caused by a pathogen or against cancer in which CD8+ T-cell responses play a protective role, wherein the kit generates a protective CD8+ T cell immune response against at least one target antigen of said pathogen or cancer;
with the proviso that if the source of epitopes in (i) is a viral vector, the viral vector in (ii) is derived from a different virus than the virus in (i).

Dependent claims 2 to 20 related to further features of the claimed use. Independent claims 21 and 26 related to recombinant epitope strings and dependent claims 22, 23 and 25 were directed to various recombinant vectors encoding the epitope string of claim 21. Independent claim 24 related to the modified virus Ankara encoding the P.falciparum antigen TRAP. Claim 27 related to a recombinant polypeptide comprising a P.falciparum antigen and a string of two or more malarial CD8+ T cell epitopes selected from specific amino acid sequences. Claim 28 was directed to the recombinant polypeptide of claim 27 wherein the antigen was TRAP.

VII. On 24 October 2008, appellant III filed further submissions as regards, in particular, the admissibility of appellant I's appeal and informed the board that it would not be represented at the oral proceedings.

VIII. In its communication dated 7 November 2008, the board informed the parties of its preliminary, non-binding opinion, in particular, that the appeal of appellant I should be admissible.

IX. Appellants I and III filed answers to the board's communication. On 21 November 2008, appellant II informed the board that it would not attend oral proceedings.

X. Oral proceedings were held on 25 November 2008 and were attended only by the representatives of Appellant I.

XI. The documents mentioned in the present decision are the following:

(2) : Chamberlain, R.S. et al., Proceedings of the American Association for Cancer Research, Vol.37, Immunology/Biological Therapy, Poster Section 10, Abstract 3263, Tuesday 23 April 1996, page 478, March 1996;

(3) : Carroll, M.W. et al., Vaccine, Vol.15, No.4, pages 387 to 394, March 1997;

(26) : WO 98/04728 published on 5 February 1998 with the filing date of 9 July 1997 and the priority date of 25 July 1996;

(29) : Leong Kah, Hoo et al., Vaccines 95, Cold Spring Harbor Laboratory Press, pages 327 to 331, 1995;

(45) : Chamberlain, R.S. et al, Poster presentation, Tuesday 23 April 1996 (corresponding to D2);

(56) : WO 96/26271 published on 29 August 1996 with the filing date of 13 February 1996 and the priority date of 22 February 1995;

(57) : Rodrigues, M. et al., The Journal of Immunology, Vol.153, pages 4636 to 4647, 1994;

(81) : Moorthy, V.S. et al., PLoS Medicine, Vol.1, Issue No.2, e33, pages 128 to 136, November 2004;

(83) : Guimaraes-Walker, A. et al., AIDS Vaccine 2004 International Conference, August 31, 2004;

XII. Appellant I's submissions in writing and during oral proceedings insofar as relevant to the present decision may be summarized as follows:

Admissibility of its own appeal

The appeal fulfilled the requirements of Articles 106 to 108 EPC, Rule 97 and Rule 99, paragraph 1 (a) to (c) and paragraph (2) EPC. In addition, evidence in the form of an enclosed extract from the Companies House register had been provided that Oxxon Therapeutics Ltd. was an existing company. Finally and in answer to appellant III's arguments as regards non-admissibility due to an alleged conflict of interest, attention was drawn to the decision T 1009/97 of 18 January 2001 where the conclusion was reached that any such potential conflict did not result in an appeal being found to be inadmissible.

Main request
Article 54 EPC; novelty of claim 1

- Document (3) disclosed a regimen of heterologous priming and boosting for immunisation which involved priming and boosting vectors with replicative abilities corresponding to those of the vectors for the claimed use, both vectors expressing the model antigen β-galactosidase. The treated mice produced increased levels of IFN-γ. When the vaccinia vector was used for priming and the fowlpox virus was used for boosting, an improvement in the immune reaction was observed compared to that resulting from a regimen of homologous

prime and boost, which improvement did not occur when the reverse combination was used.

These teachings did not affect the novelty of the claimed subject-matter for the following reasons:
- There was no mention of a CD8+ T cells immune response having occurred.
- The observed increase in IFN-γ was not indicative of such a response since it could equally be due to CD4+ T cells or NK cells.
- Under the experimental conditions chosen, it would not be expected that a CD8+ T cells immune response could have occurred.
- As the improvement in the immune response depended on which vector was used first whereas both the priming and boosting vectors expressed β-galactosidase, it must be that this improvement was not due to β-galactosidase itself. Otherwise stated, no protective CD8+ T cells immune response was triggered by β-galactosidase.

Thus, document (3) was not detrimental to the novelty of claim 1.

- Document (2) disclosed a prime-boost regimen in which the priming and boosting compositions were the same as the priming and boosting compositions of present claim 1, the model antigen being β-galactosidase. This regimen was said to induce a cytotoxic T lymphocytes (CTL) reaction. However, document (2) did not disclose the feature that a protective CD8+ T cell response was generated. Consequently, the subject-matter of claim 1 was novel over document (2).

- Document (29) was essentially concerned with antibody responses to the prime-boost regimen which it described. When and to the small extent to which a CTL response was observed, its origin (CD4+ T cells, CD8+ T cells, NK cells) had not been determined. It was not even certain whether a CD8+ T cell response would have inherently occurred in the type of mice used. The document did not provide a clear and unambiguous disclosure falling within the scope of the claimed subject-matter.

Article 83 EPC; sufficiency of disclosure

While expressing doubts that the claimed invention could not be repeated across the entire scope of the claims, appellant III had failed to substantiate these doubts by verifiable facts.
Each of the references cited by appellant III in support of its doubts referred to early stage clinical trials in humans. These aimed at a fine tuning of essential parameters in order to determine optimal conditions of treatment. Some negative results would, thus, be expected but, of course, it did not mean that the claimed use was not enabled. In fact, such negative results as described in e.g. document (81) - disclosing a prophylactic malaria vaccine trial - or in document (83) - concerning clinical trials with compositions expressing HIV antigens - could be explained by some features specific to the experimental set-up used to obtain them, e.g. the time point at which efficacy was measured, the dose of priming composition, the time elapsing between priming and boosting etc.... Later on, other post-published documents showed that the proper conditions for

achieving a satisfactory immune response could be obtained.
The skilled person would be able to reproduce the invention on the basis of the information given in the patent in suit. The requirement of Article 83 EPC was fulfilled.

Article 56 EPC, inventive step

- The closest prior art was document (57) which presented a study of the effectiveness of, in particular, several recombinant influenza and vaccinia viruses carrying the CD8+ T cell epitope of the circumsporozoite (CS) protein of Plasmodium yoelii to induce a malaria-specific immune response (pages 4639 and 4642). All recombinant influenza or vaccinia viruses had one feature in common, namely that they were life viral vectors i.e. replicative viruses (abstract). The immunisation was said to be particularly effective when an attenuated vaccinia construct was used as booster after the mice were primed with a recombinant influenza virus (passage bridging pages 4646 and 4647).

Starting from document (57), the problem to be solved was to devise a prime-boost system for generating a protective CD8+ T cell response in diseases where CD8+ T cell responses were important.
The solution provided was to prime with a non-replicative vector and to boost with a non-replicative pox-virus.

Document (57) did not suggest nor provide any motivation to change from a replicative to a non-

replicative prime/boost system. To the contrary, it was mentioned on page 4647 that the results obtained underscored the considerable potential of life carriers for the development of vaccines. The fact that an attenuated vaccinia virus had been used as a boost did not necessarily imply for the skilled person that a non-replicative vector should be used because there were many ways in which to attenuate a virus other than by affecting replication.
The combination of the teachings of document (57) with those of other documents of the state of the art did not lead in an obvious manner to the now claimed use because these other documents described prime/boost systems with a very high number of parameters which could influence the immune response. Consequently, they did not help in finding the above mentioned solution.
The claimed subject-matter was inventive over document (57).

- Earlier on in the proceedings, document (2) had been regarded as the closest prior art, as it disclosed a prime /boost regimen in which the priming and boosting vectors had the same replicative properties as the vectors of the present claimed use.

Starting from document (2), the problem to be solved could be seen in the provision of means and methods for allowing vaccination and protection against pathogens, tumors or cancer.
The solution was the use of a priming and a boosting composition for generating a protective CD8+ cell immune response.
This feature was crucial to inventive step. Although it might have been suspected that it would be advantageous

to do so, generating a protective CD8+ T cell immune response was not disclosed as a consequence of the regimen described in document (2) and, furthermore, the means and methods for obtaining it were not known. The authors of document (2) were content to have determined that heterologous boosting strategies would have more therapeutic potential than homologous boosting strategies. They had never been interested in the nature of the immune response. For this reason, there was nothing in document (2) that rendered the claimed invention obvious.

XIII. Appellant III's arguments in writing insofar as relevant to the present decision may be summarized as follows:

Admissibility of appellant I's appeal

- Before the filing of the notice of appeal in the name of the patentee Oxxon Therapeutics, opponent 03, Oxford Biomedica, had taken over Oxxon Therapeutics on 12 March 2007. Therefore, it was the case that the appeal filed by patentee on 8 June 2007 and the grounds of appeal submitted thereafter were filed by a non-existing company. Alternatively, both the notice and the grounds of appeal were filed in the name of opponent 03 and, therefore, the patentee Oxford Biomedica had not filed a valid appeal. The board must, thus, declare the appeal as filed by Oxxon Therapeutics (or Oxford Biomedica) being both patentee and opponent at the same time as inadmissible.

- The appeal stated to be of the patentee (Oxxon Therapeutics) should be declared non-valid as the

acting of the representative resulted in a conflict of interest. On 2 October 2003, this representative had filed an opposition on behalf of opponent 03, Oxford Biomedica. The opposition by opponent 06 (appellant III) was filed by another representative of the same firm. However, identical oppositions were drafted for both opponents by the representative of opponent 03 - now representing patentee - as it was not unusual for opponents to bundle their forces in this way.
It was against common law and against Art.3.2 of the EPI regulation on discipline that the same representative now represents the patentee when his office had represented and he was himself heavily involved in the representation of opponent 06 who was still involved in the proceedings.
The board must, thus, declare that neither the patentee's representative nor anyone else of the same firm should be allowed to represent Oxford Biomedica as patentee during the present appeal proceedings and, furthermore, it should decide that the appeal filed by the patentee was non-admissible.

Main request
Article 54 EPC; novelty of claim 1

Claim 1 of this request was not novel in view of documents (2), (3), (26), (29), (45) and (56). It had not been denied by the patentee that for all these documents, the only new feature would be the production of a CD8+ T cell response in case a (already described) non-replicating or replication impaired pox virus was used as the boost.

Yet, the patent did not show that the heterologous prime-boost induced a protective CD8+ T cell response only. On the contrary, a clear CTL response was induced as shown in the different examples. Therefore, it was not clear at all whether the obtained protection was the result from a CTL response or from the induction of protective CD8+ T cell responses. However, if it was assumed for the sake of argument that a CD8+ T cell response was decisive for the second medical use of the prime/boost kit as claimed indeed and that the inventors contributed the recognition thereof as a novel feature, then still based on for instance T 254/93 (OJ EPO 1998, 285), the recognition of this new mechanism could not afford novelty to these claims.

Article 83 EPC; sufficiency of disclosure

The scope of the claims was extremely broad: application of protective vaccination in any creature as for instance humans against a disease caused by any pathogen or any cancer. Documents (81) and (83) described vaccination protocols respectively against malaria and against HIV in humans. The conclusion from these publications was that the T-cell inducing vaccine was ineffective at reducing the natural infection rate in humans; the results obtained in monkeys could not be reproduced. The patentee had stated that the circumstances were suboptimal and that a detectable immune response had been observed when using a protocol involving a much higher dose of boost than was used in the examples of the protective immune response of the present patent. Therefore, a relevant teaching for generating a protective CD8+ T cell immune response had been disclosed neither in the patent itself nor in the

clinical trials published after the priority date. To reproduce the set of claims required an undue burden and the patent in suit did not meet the requirement of Article 83 EPC.

Article 56 EPC; inventive step

Document (2) was the closest prior art as it disclosed the use of a heterologous prime and boost regimen for the generation of CTL against the model tumor antigen β-galactosidase and also that such heterologous boosting strategies may have more vaccination potential than homologous boosting strategies for the development of future cancer therapies.
The technical problem to be solved based on document (2) was the provision of a heterologous vaccination strategy which was safe for mammals because it was obvious that it was the target to meet. The application of the safe MVA vector was generally known in the art. Based on document (2), it would be a logical step to apply as boost the MVA virus and therefore the proposed solution did not involve an inventive step.
In cases where the source of CD8+ T cell epitopes in the priming composition was a Ty virus-like particle or an adenovirus, inventive step was also not achieved because it such molecules had already been used in the art as epitope carriers.

- The patentee always insisted on the fact that the claims were directed to the generation of a protective CD8+ T cell immune response. The CTL assay had been used to detect cytotoxic T cell reactivity but it was not suited to identify which cells were responsible therefor, CD8+, CD4+ or NK cells. Appellant III also

added : "So, there is no indication that the CTL assays as described in the application are in fact different as compared to the CTL assays described in D2, what does not only take away the argumentation of novelty (see above) but also the argumentation relative to inventive step of the opposed patent."
The requirements of Article 56 EPC were not fulfilled.

XIV. Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed on 24 October 2008 filed under the heading "First Auxiliary Request-amended" or any of the second to sixth auxiliary requests filed with the statement of grounds of appeal or seventh to eighth auxiliary requests filed on 24 October 2008.

Appellant III requested in writing that the decision under appeal be set aside and that the patent be revoked. It further requested that the appeal by the patentee be declared inadmissible and that the patent attorneys of the office of Carpmaels and Ransford be no longer allowed to represent any of the parties involved in proceedings relating to the present patent EP 979 284, and the divisional patents EP 1 335 023, EP 1 589 108 and 1616 954.

Reasons for the decision

Procedural matters
Admissibility of the appeal filed by appellant II, PowderJect Vaccines Inc.

1. Appellant II appealed the decision of the opposition division of 31 January 2007 on 5 April 2007 and paid the appeal fee on the same day. However, no statement setting out the grounds of appeal was filed. The notice of appeal contains nothing which could be regarded as constituting grounds of appeal.

2. In the present case the provisions of the EPC 1973 on the assessment of the admissibility of the appeal are to be applied. For the reasons determining the board's finding in this respect, it is referred to decision J 10/07, OJ EPO 2008, 567, points 1 et seq. of the reasons. In this decision, the Legal Board of Appeal explained in detail why the provisions of the EPC 1973 are to be applied on the assessment of the admissibility of an appeal if the time limit for setting out the grounds of appeal had already expired when the EPC 2000 came into force.

3. Pursuant to Article 108, third sentence, EPC 1973 in conjunction with Rule 65(1) EPC 1973, the Board of Appeal shall reject the appeal as inadmissible, if no grounds of appeal have been filed before the expiry of the time limit laid down in Article 108, third sentence, EPC 1973. Such is the case here.

Admissibility/validity of the appeal filed by appellant I, the patent proprietor Oxxon Therapeutics, and identification of which company is now appellant I

4. One month before the oral proceedings before the board appellant III, Danisco (former Genencor), raised an objection against the admissibility of the appeal filed by appellant I, the patent proprietor Oxxon Therapeutics. The objection was based on the allegation that as a result of Oxxon Therapeutics having been taken over by Oxford BioMedica on March 12 2007, i.e. before the present appeal was filed, the appeal had been filed by a non-existing party. Following an invitation by the board to file evidence showing that Oxxon Therapeutics still exists as a legal person or, in case of a universal succession (e.g. a merger) having taken place, which company is the legal successor of Oxxon Therapeutics, appellant I submitted a print-out from the Companies House Register in which the status of Oxxon Therapeutics Limited, i.e. of appellant I, is stated as "active".

5. Appellant III based its allegation that Oxxon Therapeutics had ceased to exist on a news release dated 12 March 2007. However, that news release only mentions that Oxford BioMedica (opponent 03) had acquired the patent proprietor company. It contains no information to the effect that the acquisition took place in the form of a merger or any other form of universal succession entailing as a consequence that appellant I would have ceased to exist. As the print-out from the Companies House Register submitted by appellant I confirms, appellant I is still an active company. There are therefore no doubts that the appeal has been validly filed by Oxxon Therapeutic Ltd. being an existing legal

person and that that company continues to be the appellant I in the present appeal proceedings.

Exclusion of representatives from representation

6. Appellant III alleged the existence of a conflict of interest in the person of the representative having formerly represented appellant III (opponent 06) and formally still representing opponent 03 and now representing appellant I, the patent proprietor. The board notes first of all that even though the representative has not formally withdrawn from representation as regards opponent 03, he has not acted for opponent 03 in the present appeal proceedings. Opponent 03 is only a party as of right and has not taken position in the appeal proceedings, i.e. after having acquired the patent proprietor, which appears perfectly normal in the circumstances.

7. Appellant III did not indicate on which legal basis the board could be entitled to accede to its request and exclude the representatives of the office of Carpmaels and Ransford from further representing any of the parties, in particular appellant I, the patent proprietor, and the board also sees none.

8. The existence of a conflict of interest, if any, concerns the relation between the representative and his client and may, depending on the circumstances of the case, entail disciplinary measures being taken against the representative under the Regulation on discipline. This would not be a matter for the board.

9. By contrast, the validity of procedural acts undertaken by the representative for his client is not affected by the existence of a conflict of interest. Nor is there any legal basis for excluding a professional representative whose name appears on the list of professional representatives from representing a party in proceedings before the EPO (see also T 1009/97, supra; Headnote and point 2 et seq. of the Reasons). On the contrary, Article 134(5) EPC stipulates that persons whose names appear on the list of professional representatives shall be entitled to act in all proceedings established by the EPC. So are the representatives of the office of Carpmaels and Ransford.

Substantive matters
Article 54 EPC; novelty of claim 1 of the main request filed as "First Auxiliary Request- amended" on 24 October 2008.

10. The teachings of documents (3), (2), (45), (29), (26) and (56) were argued to be detrimental to novelty. In the following, their relevance will be assessed in the given order.

11. Document (3) teaches the use of a priming composition made of a non-replicating recombinant vaccinia virus expressing the model tumor associated antigen β-galactosidase (MVA-LZ) and of a boosting composition comprising the non-replicating recombinant fowlpoxvirus vector FPV.bg40k also expressing β-galactosidase, for the production of a potential anti-cancer vaccine (page 390).

12. Appellant I readily agreed that the replicative abilities of these two vectors were the same as those of

the vectors contained in the prime/boost compositions for the now claimed use. The question relevant to novelty is whether or not the skilled person would regard the teaching of document (3) as a teaching - explicit or otherwise - of a regimen whereby the antigen used would trigger a CD8+ T cell immune response. It is without doubt that no reference at all is made in document (3) to such a response having taken place. For the skilled person, would it then be implicit that it did ?

13. Document (3) discloses that spleenocytes from mice primed with MVA-LZ reveal elevated levels of e.g. IFN-γ (page 390, passage bridging the left- and right- hand columns). Furthermore, an experiment was carried out to compare the efficiency of homologous versus heterologous boosting. It led to the result that heterologous boosting is more efficient, at least in the experimental set-up where MVA-LZ is used for priming and FPV-bg40k is used for boosting. The reverse combination, however, does not generate any improvement in the immune response, notwithstanding that both vectors express β-galactosidase (page 390, right-hand column).

14. Together with its statement of grounds of appeal, appellant I produced a diagram showing that the capacity of inducing cytokine secretion, e.g. IFN-γ , belonged not only to CD8+ T cells but also to CD4+ T cells and NK cells, a point which was not challenged by appellant III in its comments on appellant I's grounds of appeal of 3 March 2008. Thus, the production of IFN-γ observed in the experiments carried out in document (3) does not constitute a satisfactory albeit indirect proof that a CD8+ T cell immune response has taken place.

15. As for the observation that improvement of the immune response **will or not** be achieved depending on the order in which the vectors are used, β-galactosidase being in any case expressed, it is possible to consider it as evidence that, when observed, the improvement is not due to the presence of β-galactosidase. Otherwise stated, this observation suggests that β-galactosidase does not contain "effective" CD8+ T cell epitopes in the given experimental circumstances since such epitopes would be expected to contribute to the improvement. In this context, it is worth mentioning that the statement at the end of the second full paragraph on page 390, right-hand column:

"Due to the aggressive nature of the tumor it is perhaps not surprising that treatment at a relatively late stage of tumor growth would not have a dramatic effect on survival even if heterologous boosting was advantageous."

is not sufficiently clear to have any kind of bearing – positive or negative- on the findings above.

16. In its letter dated of 3 March 2008 - dealing with the novelty issue -, appellant III did not argue that a CD8+ T cell immune response took place in any of the experiments described in the documents of the prior art, nor that it might have been a matter of common general knowledge that it would. The arguments rather went to the fact that the patent in suit did not demonstrate a CD8+ T cell immune response in any of the examples given. Of course, this may be of relevance to sufficiency of disclosure, but it does not change any of the findings

in points 5 and 6 supra as regards the implicit teaching of document (3).

17. For these reasons, the board concludes that the skilled person would not have found in document (3) the explicit or implicit teaching of a CD8+ T cell immune response. Novelty is, thus, acknowledged.

18. Documents (2) and (45) provide the same teaching, the earlier being the published abstract of part of the content of the latter, a poster presentation. Both teach that heterologous boosting is better than homologous boosting to generate an immune response. Prime/boost vectors are tested, which possess the same replicative properties as those of the vectors for the now claimed use. In document (45), reference is made to two model antigens, β-galactosidase and influenza nucleoprotein which are shown to generate an antibody response and a CTL response. However, the origin of the CTL response (CD8+ T cells, CD4+ T cells, NK cells) is not investigated. There is, thus, no clear and unambiguous disclosure of CD8+ T cells being involved in the immune response. Novelty is not affected by any of these documents.

19. Document (29) is concerned with studying antibody immune responses arising from a vaccination regimen comprising vectors with the same replicative abilities as the vectors for the now claimed use, the antigen being the hemagglutinin antigen of influenza virus. A reference to CTL responses is made on page 329:

"Although primary CTL responses against HA could not be demonstrated with one immunization, moderate CTL

responses were obtained in primed spleen cells upon restimulation with influenza virus in vitro."

In the board's judgement, this statement falls well short of a clear and unambiguous disclosure that a CD8+ T cell immune response has taken place. For this reason and in accordance with the case law (T 509/04 of 5 July 2005 and T 836/01 of 7 October 2003), this document is not considered as relevant to novelty.

20. Document (26) is state of the art for the purpose of assessing novelty under Article 54(3) EPC 1973. It is concerned with the isolation of recombinant pox viruses capable of expressing cell-encoded tumor associated antigens e.g. gp100 and MART-1. Replicating vaccinia viruses and non-replicating fowlpox viruses are disclosed on page 7 as "useful in practising the present invention". The passage bridging pages 10 and 11 which is the only one dealing with prime/boost vaccination regimens reads as follows:

"A specific immune response to a tumor associated antigen can be generated by administering between about 10^5-10^9 pfu of the recombinant pox virus .... The boosting antigen may preferably be administered using a second pox virus vector from a different pox genus..."

There is no mention in the document of the kind of immune responses to be expected, let alone of a CD8+ T cell immune response. The examples provided describe the isolation of specific vectors but not their use. In the board's judgement, the teachings of this document as regard vaccination with viral vectors are simply much too vague to be affecting novelty.

21. Document (56) teaches that human cytotoxic T cells may be generated where a sufficient amount of recombinant pox virus vector carrying the relevant antigen is introduced into a host and the host is thereafter contacted with additional antigen expressed from a second pox virus different from the first one. On pages 10 and 11, information is given as to which sites on the pox virus vector should be used to insert the DNA encoding the antigenic sequence without affecting viral viability. The prime/boost immunization protocols tested involve the recombinant vaccinia-CEA viral vector either for priming or for boosting (see e.g. Table 6). This vector is listed on page 15 amongst the pox viruses of interest and these are all life viral vectors. If only for this reason, document (56) is not novelty destroying for the subject-matter of claim 1 which is limited to non-replicative vectors. It must also be noted that no mention is made in document (56) of the cytotoxic response being due to CD8+ cells.

22. For the reasons given in points 11 to 21 supra, novelty is acknowledged.

Sufficiency of disclosure

23. Appellant III argued lack of sufficient disclosure on the basis of post-published documents (81) and (83). Document (81) is concerned with a vaccine efficacy trial against malaria infection. This trial involves a prime/boost regimen with DNA prime vectors and MVA viral boost vectors expressing an antigenic peptide comprising, amongst others, 14 CD8+ T cell epitopes (page 129). On page 128, it is stated that:

"DNA/MVA prime-boost vaccination is safe and highly immunogenic for effector T-cell induction in a malaria endemic area. But despite having produced a substantial reduction in liver-stage parasites in challenge studies of non-immune volunteers, this first generation-cell inducing vaccine was ineffective at reducing the natural infection rate in semi-immune African adults."

And on page 134:

"Second-generation prime-boost vaccine strategies for malaria currently in or near to clinical evaluation include the following: use of a different viral vector as the priming agent that may lead to proportionately greater CD8+ rather than CD4+ T cell induction..."

Document (83) is concerned with a vaccine efficacy trial against HIV infection. HIV specific CD8+ immune responses are observed in 18% of all vaccinated volunteers.

In short, documents (81) and (83) confirm the role of CD8+ T cells in generating a immune response against malaria or HIV disclosed in the patent in suit.

24. It cannot be denied that the results obtained in field trials are not perfect as they do not show absolute protection against the disease. However, in accordance with the case law (e.g. T 315/03, OJ EPO 2006, 15), no such stringent criteria need be fulfilled for sufficiency of disclosure to be acknowledged. On the contrary, it is enough that on the basis of the information given in the patent, one may reasonably

assume that the claimed use may be carried out. Of course, one will expect that further work be required to adjust to real life conditions but, unless proven otherwise, this work is considered of a routine kind well within the capacities of the skilled person.

25. The patent in suit (e.g. Examples 1 and 6 illustrating the invention in mice and chimpanzees) describes the involvement of CD8+ T cells in the protective immune response observed with prime/boost regimens comprising a source of malarial or HIV epitopes carried by non-replicative vector/non-replicative pox virus vector. The reproducibility of the assay (Elispot assay) which needs to be carried out to identify suitable CD8+ T cell epitopes has not been challenged.

26. For these reasons, sufficiency of disclosure is acknowledged.

Article 56 EPC; inventive step

27. In accordance with the case law (e.g. T 606/89 of 18 September 1990), the closest prior art is generally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common. The closest prior art must, thus, be a document which describes the induction of a CD8+ T cell protective immune response in a vaccination regimen, i.e. as already mentioned in the board's communication under Article 15(1) RPBA, document (57).

28. Document (57) is concerned with testing the effectiveness of several recombinant influenza and vaccinia viruses to induce a malaria specific immune response which is quantitatively evaluated with regard to epitope-specific humoral and CD8+ T cell responses and their capacity to confer protection against malaria. On page 4637, the authors explain that their primary aim had been to evaluate the worth of life viral vectors in vaccination regimens and, indeed, all recombinant viruses tested – even when attenuated – are life viral vectors. The results obtained show that comparable levels of epitope-specific CD8+ T cells are induced by influenza and vaccinia vectors carrying the entire circumsporozoite protein of Plasmodium yoelii or a small sequence representing only the T cell epitope (page 4646). Protective immunity – measured as the inhibition of liver stage development of malaria parasites – is enhanced when priming with recombinant influenza viruses is followed by boosting with recombinant vaccinia (page 4644). Interestingly from the point of view of vaccine development, when a highly attenuated recombinant vaccinia virus is used as a boost, 81% of the mice are fully resistant to malaria challenge (passage bridging pages 4646 and 4647). In the discussion section of the article, it is mentioned on page 4647:

"The fact that a highly attenuated recombinant vaccinia virus expressing a key malaria Ag is highly immunogenic makes this vector an attractive and viable vaccine candidate for human use."

and it is concluded as follows:

"From a more general point of view, our results underscore the considerable potential of life carriers for the development of vaccines".

29. Starting from the closest prior art, the problem to be solved may be defined as the provision of a further prime/ boost system for generating a protective CD8+ T cell immune response.

30. The solution provided is the prime/boost system of claim 1, making use of non-replicative vectors/non-replicative pox virus vectors to carry the antigen bearing CD8+ T cell epitopes.

31. Document (57) does not suggest such a prime/boost regimen. In fact, in the light of its teachings which emphasize the potential of life viral vectors, the skilled person would have rather been motivated to test further different prime/boost regimens involving life viral vectors. In view of the obvious advantages of attenuated life viral vectors in terms of safety – mentioned in document (57) –, he/she may have chosen to devise prime/boost systems with attenuated viral vectors. This, however, does not amount to choosing vectors which are non-replicative because attenuation may be achieved in many different ways – as shown in document (57) itself. Thus, document (57) on its own does not render obvious the claimed subject-matter.

32. Other documents of the state of the art do not specifically deal with an immune response due to CD8+ T cells and, therefore the combination of document (57) with either one of them cannot render the claimed invention obvious.

33. For these reasons, inventive step is acknowledged.

34. For sake of completeness, the relevance of document (2) for inventive step will also be reviewed as document (2) was considered to be the closest prior art in the earlier stages of the proceedings. Document (2) is a very short abstract which teaches the use of non-replicating vectors in prime/boost regimens for vaccination purposes (see point 18, supra). Various regimens are tested for their ability to induce a CTL reaction. The technical feature that the prime/boost combinations generate a protective CD8+ T cell immune response is not disclosed. No evidence has been provided that the skilled person would necessarily come to the conclusion that they did.

35. In the board's judgement, it would be an obvious desideratum when developing a vaccination protocol to achieve as high a level as possible of immune responses of all kinds. And, indeed, this is reflected in document (2) and the other documents of the state of the art by the fact that they teach to measure "generic" cytolytic activity - generated by CD8+ T cells but also CD4+ T cells and NK cells - as well as antibody responses as parameters reflecting the effectiveness of the vaccination regimen. Thus, it is only with the hindsight knowledge of the invention that this "generic strategy" can be regarded as making obvious the "specific strategy" of preferentially inducing CD8+ T cell immune responses. Document (2) does not affect the inventive step of the claimed subject-matter.

36. In its submissions dated 3 March 2008 in response to appellant I's statement of grounds of appeal, appellant III refers to its arguments against inventive step elaborated for the auxiliary request accepted by the opposition division as equally valid for the requests filed on appeal. These arguments presented on 11 June 2007 all deal with the obviousness of using the specific vectors MVA virus, Ty virus-like particles or adenovirus in the priming compositions. They are not relevant to present claim 1 which is not directed to the use of such specific priming compositions.

37. The objection was also raised that the CTL assays described in the patent in suit were not suited for distinguishing between CD8+ T cells, CD4+ T cells or NK cells. This is certainly true but in the patent in suit, the characterisation of the CD8+ T cells response is not made on the basis of a CTL assay but on the basis of the Elispot assay.

38. For the reasons given in points 27 to 32 supra, the requirements of Article 56 EPC are fulfilled.

Order

For these reasons it is decided that:

1. The appeal filed by the appellant PowderJect Vaccines Inc. is rejected as inadmissible.

2. The request filed by the appellant Danisco US, Inc. that the patent attorneys of Carpmaels and Ransford be excluded from further representing any of the parties in proceedings relating to the patent-in-suit EP 979 284 is rejected.

3. The decision under appeal is set aside.

4. The case is remitted to the opposition division with the order to maintain the patent with the claims of the main request of 24 October 2008, said claims having been filed as "First Auxiliary Request- amended", and a description and drawings to be adapted thereto.

The Registrar The Chairman

A. Wolinski L. Galligani