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D E C I S I O N
of 18 April 1996

Case Number: T 0339/93 - 3.3.4

Application Number: 82402380.8

Publication Number: 0083286

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:
Modified vaccinia virus and methods for making and using the same

Patentee:
HEALTH RESEARCH, INCORPORATED

Opponent:
Katinger, Prof. Dr. H. Universität für Bodenkultur Institut für angew. Mikrobiologie

Headword:
Modified vaccinia virus/HEALTH RESEARCH, INC.

Relevant legal provisions:
EPC Art. 54, 56, 99, 114(2), 111(1)

Keyword:
"Admissibility of opposition - yes - no doubt as to opponent"
"Reference to Enlarged Board of questions on admissibility - no"
"Admissibility of the appeal - yes; novelty - yes"
"Inventive step of main and first auxiliary request - no"
"Second auxiliary request - no unambiguous basis"
"Third auxiliary request referred back to the first instance"

Decisions cited:
T 0289/91, T 0590/93, T 0635/88, T 0548/91

Catchword:
True identity of opponent held established, thus no reason to refer questions to Enlarged Board of Appeal. Remittal of third auxiliary request to first instance appropriate in this case, so that parties can direct their arguments knowing reasoning on which other requests refused.

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Case Number: T 0339/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 18 April 1996

Appellant: (Opponent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office dated 9 February 1993 rejecting the opposition filed against European patent No. 0 083 286 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 083 286 based on European patent application No. 82 402 380.8 and relating to "Modified vaccinia virus and methods for making and using the same" was granted for eleven Contracting States, with fourteen claims.

Claims 1, 10 and 14 of the granted patent read as follows:

"1. A recombinant vaccinia virus characterized in that it contains in a non-essential region of the vaccinia genome a DNA segment which does not naturally occur in vaccinia viruses and which

(a) is expressed in a vaccinated mammal and encodes an antigen which is capable of inducing an antibody-response, or

(b) is expressed in infected eukaryotic cells or host organisms and encodes an antigen or a biological product other than an antigen or

(c) is capable of modifying, replacing or repairing defective genes in the infected eukaryotic cell or organism.

10. A method for preparing a recombinant vaccinia virus according to anyone of claims 1 to 4, which method comprises infecting a cell with a vaccinia virus in a cell-compatible medium in the presence of donor DNA molecules, said donor DNA molecules comprising a DNA segment not naturally occurring in vaccinia virus flanked by DNA sequences homologous with portions of a DNA sequence present in the vaccinia virus.

14. A vaccine comprising a recombinant vaccinia virus according to any one of claims 1 to 4."

Dependent claims 2 to 4 specified further features of the DNA segment to be included in the vaccinia viral DNA.

Claims 5 to 9, and 11 to 13 related to methods of use and preparation of the vaccinia virus of claims 1 to 4.

II. An opposition was filed asking for revocation of the patent in its entirety on the grounds of Article 100(a) EPC (lack of novelty and inventive step) and Article 100(b) EPC (insufficiency of disclosure), relying *inter alia* on the following documents:

(1) Sam C.K. and K.R. Dumbell, Ann. Virol. (Inst.Pasteur), 1981, no. 132E, pp. 135-150

(2) Nakano E. et al., Abstract W36/09 from the Abstracts of the Vth International Congress of Virology, Strasbourg, France, August 2-7, 1981

(11) Panicali D. et al., Journal of Virology, 1981, vol. 37, No. 3, pp. 1000-1010

III. Oral proceedings before the Opposition Division took place on 14 January 1993. During the oral proceedings, the Patentee requested for the first time that the opposition should be rejected as inadmissible because it had been filed on behalf of a third party. The Opposition Division decided to reject this request under Article 114(2) EPC since it had been submitted too late into the proceedings, and the evidence presented was not considered sufficient to enable the

Opposition Division to take a decision without adjourning the proceedings, and held that the opposition was admissible as it met all the requirements of Article 99(1) and 100 EPC and of Rule 55 EPC.

The requests regarding lack of novelty (Article 100(a) EPC) and insufficiency of disclosure were dropped at the beginning of the oral proceedings.

IV. By a decision dated 9 February 1993, the Opposition Division maintained the patent as granted.

Despite the objections to sufficiency and novelty not being maintained, the Opposition Division in its written decision made the comments:

- The objection of insufficiency of disclosure could not be upheld in view of the several examples provided by the description which showed the capability to express foreign genes from the recombinant vaccinia viral vectors.

- Novelty had to be acknowledged in view of the statement in document (1) itself that "RP (i.e. rabbit pox virus) is sufficiently closely related to be regarded as a subspecies of vaccinia." Thus the rabbit pox virus could not be regarded as being "foreign" DNA with respect to vaccinia virus.

- The closest prior art was identified as document (2). It was decided that said document, whether taken alone or in combination with any other document of the state of the art, did not suggest that foreign DNA could be expressed from a vaccinia viral vector and, therefore, inventive step was acknowledged.

V. The Appellant (Opponent) lodged an appeal against the decision of the Opposition Division on the sole ground that the claimed invention lacked inventive step, and submitted a declaration explaining that as head of a research team in this field, who would wish to obtain support for his research in return for providing knowhow, he had a personal interest in preventing the existence of a blocking patent, and that he personally had instructed the filing of the opposition.

VI. Further submissions and documents were received from both parties, and a communication was sent by the Board according to Article 11(2) of the rules of procedure of the Boards of Appeal, setting out the Board's preliminary position. Of these documents the following are referred to in this decision:

(23) Declaration of Keith R. Dumbell filed on 18 March 1996.

(24) Taylor J. and E. Paoletti, Prog. Vet. Microbiol., Immun., 1988, vol. 4, pp. 197-217

VII. Oral proceedings were held on 18 April 1996. During these proceedings, the Respondents made the request that if the Board decided not to find the appeal inadmissible because the opposition was inadmissible, the two following questions should be referred to the Enlarged Board of Appeal:

Is an opposition admissible if it was filed by a third party upon request of another party desiring to remain anonymous ?

What is the level of evidence required from the Patentee for the Board to request that the Opponent states affirmatively that he is not a dummy in a sworn statement in accordance with Article 117 EPC ?

VIII. During the course of the oral proceedings, apart from arguments in support of their main request that the appeal be dismissed, the Respondents also submitted three auxiliary requests, of which the respective Claims 1 are set out below with additions to the claim 1 as granted marked by bold print. Claim 1 of auxiliary request I read as follows:

"1. A recombinant vaccinia virus characterized in that it **stably** contains in a non-essential region of the vaccinia genome a DNA segment which does not naturally occur in vaccinia viruses and which

(a) is expressed in a vaccinated mammal and encodes an antigen which is capable of inducing an antibody-response, or

(b) is expressed in infected eukaryotic cells or host organisms and encodes an antigen or a biological product other than an antigen or

(c) is capable of modifying, replacing or repairing defective genes in the infected eukaryotic cell or organism,

and in that it is obtainable by incorporating said DNA sequence by recombination using DNA molecules comprising the DNA segment flanked by DNA sequences homologous with defined portions of a DNA sequence present in the vaccinia virus."

Claim 1 of auxiliary request II read as follows:

"1. A recombinant vaccinia virus characterized in that it **stably** contains in a non-essential region of the vaccinia genome a DNA segment which does not naturally occur in vaccinia viruses and which

(a) is expressed in a vaccinated mammal **under vaccinia control** and encodes an antigen which is capable of inducing an antibody-response, or

(b) is expressed in infected eukaryotic cells or host organisms **under vaccinia control** and encodes an antigen or a biological product other than an antigen or

(c) is **under vaccinia control and** capable of modifying, replacing or repairing defective genes in the infected eukaryotic cell or organism."

Claim 1 of auxiliary request III was directed to a vaccine comprising a recombinant vaccinia virus limited to the characteristic (a) of the claim 1 as granted, and read:

"1. **A vaccine comprising** a recombinant vaccinia virus characterized in that it **stably** contains in a non essential region of the vaccinia genome a DNA segment which does not naturally occur in vaccinia viruses and which is expressed in a vaccinated mammal and encodes an antigen which is capable of inducing an antibody response, **said virus being obtainable by incorporating said DNA sequence by recombination using DNA molecules comprising the DNA segment flanked by DNA sequences homologous with defined portions of a DNA sequence present in the vaccinia virus.**

Claims 2 to 4 of auxiliary request III were directed to the vaccine of claim 1 and specified the origin of the sequences comprised within the DNA segment.

IX. The arguments submitted by the Appellant in writing and during oral proceedings can be summarized as follows:

- In reply to the Respondents's argument that the opposition should be found inadmissible, the Appellant argued that the question of admissibility had already been dealt with in the decision of the Opposition Division. No separate appeal had been filed against this part of the decision. Therefore, the question of admissibility should not form part of the appeal proceedings. Furthermore, the Appellant had filed a declaration confirming that he had instructed the opposition and explaining his personal interest in the case. Finally, account should be taken of decisions T 0289/91 (OJ EPO 94, 649) and T 0590/93 (OJ EPO 95, 337) which defined the crucial question to be answered with regard to admissibility as whether or not the identity of the opponent had been initially declared and maintained throughout the entire proceedings beyond all reasonable doubt.

- Document (1) disclosed vaccinia viruses which had integrated rabbit pox DNA into their genomes. It was novelty destroying for the subject-matter of claim 1 in the case where rabbit pox viruses were not to be considered as vaccinia viruses. Alternatively, if rabbit pox viruses were to be considered as vaccinia viruses, document (1) was novelty destroying for the subject-matter of claim 1 because it disclosed that rabbit pox viruses could be obtained which contained a DNA sequence from ectromelia viruses as foreign genetic material.

- As evidence that the concept of isolating a vaccinia viral vector existed in the art before the priority date of the patent in suit, a further document: an affidavit by Prof. Paoletti before the Canadian Patent Office relating to an interference case, was also introduced into the proceedings.

- The closest prior art was document (2). It disclosed that marker rescue of vaccinia DNA fragments into a smaller vaccinia variant genome occurred, providing that the flanking sequences of the fragments were homologous to some portion of the vaccinia genome. It provided a clear incentive for attempting to establish a vaccinia virus cloning system since it stated that: " ...it raises perhaps the more exciting aspect of utilizing poxviruses as vectors for foreign DNA."

- Taking the combined teachings of documents (1) and (2), that vaccinia viral DNA could enter homologous recombination and that foreign DNA could be introduced into and expressed from a virus which was nearly to identical to vaccinia virus, it became obvious that a recombinant vaccinia virus as claimed could be isolated which carried and expressed a foreign DNA fragment.

X. The arguments submitted by the Respondents in writing and during oral proceedings can be summarized as follows:

- The opposition should be found inadmissible as it had been filed in the name of a dummy. At a scientific meeting, the Appellant had told one of the inventors of the patent in suit that he had filed the opposition on behalf of a third party. Furthermore, in his statutory declaration, the Appellant only declared that he had a personal interest in the

opposition and not, that he had not appealed on behalf of a third party. Finally, decision T 0635/88 (OJ EPO 93, 608) was cited as defining one of the prerequisites for an opposition to be admissible as being that no reasonable doubt existed relating to the identity of the real opponent.

- Document (1) disclosed vaccinia virus temperature sensitive mutants which had been rescued for growth at 40°C by the insertion and expression of rabbit pox DNA into their genome. Temperature sensitive mutants could only be obtained in genes which are essential to the virus. It followed therefrom that the rabbit pox DNA had been inserted into an essential region of the vaccinia viral genome. Accordingly, the recombinant vaccinia virus could not be novelty-destroying for the subject-matter of claim 1, which specified that the insertion of foreign DNA must occur in a non-essential region of the genome.

- In the same manner, the experiments in document (1) allegedly disclosing the introduction of ectromelia DNA into rabbit pox viruses could not be novelty destroying, even if it was accepted that rabbit pox viruses were vaccinia viruses. This was because a close scrutiny of these experiments revealed that they were absolutely inconclusive as to whether recombination had taken place between the two viral genomes.

- An experiment was reported showing that viable rabbit pox viruses could be obtained following the uptake of rabbit pox DNA and ectromelia viruses into cell monolayers. After successive cycles of purification of the viral progeny at 40°C, three viruses had been studied which were identified as rabbit pox viruses. None had acquired the ectromelia ability to produce haemagglutinin i.e. none were recombinants.

- On the contrary, the results purportedly showing that recombination could take place between rabbit pox and ectromelia viral DNAs were based on an experiment where the successive cycles of viral purification had not been performed. Thus, it could not be ruled out that the so-called recombinants were pseudotypes, namely a virus having only a single viral genome but having incorporated in the virus the protein, but not the gene, for haemadsorption, or a mixture of rabbit pox virus with contaminant ectromelia viruses.

- Furthermore, the viral progeny derived from the rescue of cleaved rabbit pox DNA with intact ectromelia DNA in the presence of ectromelia viruses provided either no plaques or very few plaques. The DNA of these rescued viruses was never characterized. Thus, there might have been contaminants.

- There was no incentive in the art to address the problem of making vaccinia viral vectors, as the statement in document (2) that the work presented therein "raises perhaps the more exciting the aspect of utilizing poxviruses as vectors for foreign DNA" was to be understood as meaning that the problem may or may not be approached by the method disclosed in said document.

- Document (2) which was supposed to be the closest prior art document had gaps: it did not disclose the incorporation of foreign genes, neither, of course, that the foreign genes to be inserted should be flanked with homologous sequences. No information on the stability of the recombinants was given. Yet, it would be expected that the recombinant S (small) virus having inserted L (large) DNA would be unstable as the natural instability of L vaccinia variants was known in the art (document (11)).

- Nor does document (2) disclose the sites, if any, in vaccinia for stably integrating foreign DNA. It provides no guidance on whether foreign genes incorporated in vaccinia virus would be expressed when the vaccinia virus replicated in the cytoplasm, nor on whether an immune response would occur. Also document (2) did not provide a method of getting the foreign DNA into the big vaccinia virus which was too large for its DNA to be handled by restriction enzyme technique. The methods of the patent were required to solve this problem, and thus the product of these inventive methods was also inventive.

- Document (1) could not be relied on to fill the gaps in the disclosure of document (2), as the former did not suggest fitting foreign DNA with flanking sequences, did not show recombination and, a fortiori, did not provide any information on the stability of potential recombinants.

- Accordingly, the combined teachings of documents (1) and (2) would not have raised in the skilled person any reasonable expectation of success that recombinant viruses as now claimed could be isolated.

XI. The Appellant requested that the decision under appeal be set aside and that the European patent be revoked.

XII. The Respondents requested as preliminary request that the appeal be rejected as inadmissible on the ground that the opposition was inadmissible, or failing this that the Board refer the two questions submitted at the oral proceedings on 18 April 1996 to the Enlarged Board, and as main request that the appeal be dismissed

and as auxiliary requests that the decision under appeal be set aside and the patent be maintained on the basis of the set of claims filed as first, second or third auxiliary request respectively at the oral proceedings on 18 April 1996.

Reasons for the Decision

Admissibility of opposition and appeal

1. The Opposition Division had decided that the opposition was admissible, yet the Respondents again disputed this before the Board without themselves appealing. The Respondents relied on decision T 289/91 (OJ EPO 1994, 649, see point 2.1) which had said that an objection that the opposition is inadmissible, in that case also because the opponent was not entitled to file an opposition, could be raised at any stage of the proceedings, i.e. even at a late stage before the Board of Appeal, because the admissibility of the opposition was an indispensable procedural requirement for any substantive examination of the opposition submissions, and must therefore be examined by the EPO of its own motion. The Respondents also relied on the fact that as the Opposition Division upheld the patent as granted in accordance with their main request, they were not adversely affected for the purpose of Article 107 EPC and thus were neither entitled nor obliged to file an appeal to raise this issue of admissibility. The appellants asked that this challenge to the admissibility of the opposition, and hence the admissibility of the appeal, be found inadmissible by the Board.

2. For the Board to follow the request of the appellants, to find inadmissible the challenge itself to the admissibility of the opposition, would be a departure from what has been decided in previous cases. To ensure uniform application of the law, such departure should not take place without referring the question of the admissibility of the challenge to the Enlarged Board of Appeal. However the answer of the Enlarged Board would be neither necessary nor decisive for the outcome of this case, if this Board can come to the conclusion on the facts that the opposition is admissible. Accordingly the Board will first consider admissibility on the facts.

3. Article 99(1) EPC states that any person may give notice of opposition. There is no requirement that he have an interest. It is already a gloss on this to require that such person file the opposition in his own name, but following decision T 289/91 the Board is prepared to assume that the true identity of the opponent must be stated.

4. Here on the evidence the Board has no doubt that the named opponent is the true opponent. The board has had the benefit of a declaration from the opponent explaining the circumstances, and finds this borne out by the Respondents' witnesses themselves. As decision T 289/91 relied on by the Respondents makes clear, the Board can only ask for clarification by declaration if there are concrete grounds for believing that the identity of the opponent was in doubt, as was the case considered in decision T 635/88 (OJ EPO 1993, 608), where a third party had stated in writing that it was the opponent. The presumption that the named opponent is the true opponent is a strong one. Further in case T 590/93 (OJ EPO 1995, 337) the Board held that it followed from the expression "any person" in Article 99(1) EPC that the EPO was fully entitled to

take declarations of identity at their face value and was not obliged to make enquiries into the opponent's real identity by questioning the veracity of his declaration. Hearsay evidence, as given here by one inventor, that the opponent apologized to him for filing the opposition because of a specific third party, is not such a concrete ground. The precise wording used is in dispute, but the Board finds that this incident merely shows that the Appellant did file the opposition, albeit possibly at the urging of that specific third party.

5. The evidence that the opponent and the specific third party are represented by the same attorneys does not serve to throw any doubt on the identity of the opponent. One can file an opposition, but would still like to persuade others to assist in substantiating it and possibly paying any legal costs. An opposition is not assignable as such, so that it and any appeal must usually be continued in the name of the original opponent, even if others may later have a greater interest in the outcome.

6. The Respondents seem rather to be arguing for a requirement going far beyond that of Article 99 EPC, namely that it must be shown that the person with the greatest interest filed the opposition. There is no warranty for such a requirement in the European Patent Convention.

7. As there might conceivably be a need for identifying hidden opponents who were contractually debarred from filing an opposition, the Respondents were asked by the Board whether the alleged true opponent, the specific third party, would have been under some contractual obligation not to oppose the patent. The answer was no.

Thus no exceptional circumstances exist here, that might possibly make further investigation necessary on some ground of public policy of seeking to ensure the fulfilment of contracts.

8. In the circumstances the Board concludes that the opposition is admissible, and that neither the questions put forward by the Respondents nor any others need be put to the Enlarged Board to resolve this case. The request by the Respondents to refer its two questions to the Enlarged Board of Appeal is rejected.

Late filed documents

9. Six documents were filed during the written part of the appeal procedure which help in understanding the nature of the invention and the state of the art relating to vaccinia viruses. The Board decides to allow them into the proceedings. One further document was filed by the Appellant at oral proceedings (section IX, **supra**). After considering it, the Board came to the conclusion that it was not of any relevance and, therefore, decided to make use of its discretion under Article 114(2) EPC to refuse the request that it should be introduced into the proceedings.

Main request

Novelty (Article 54 EPC)

10. During the oral proceedings before the Opposition Division, the Appellant (then Opponent), as appears from the minutes, dropped his novelty objection once the Opposition Division had stated that it was evident that the subject matter of the requests before them had not been disclosed in the prior art, and also withdrew his objection under Article 83 EPC. The Opposition

Division nevertheless in its decision indicated the basis on which it acknowledged that novelty over document (1) existed. While the Board agrees with the conclusion that novelty over document (1) exists, the Board does so on different reasoning. As this document (1), and the reasons why it does not destroy novelty, also need to be taken account of when considering inventive step, it appears convenient first to give the reasoning on which novelty exists.

11. The Opposition Division based its assessment of novelty over document (1) on the assumption that rabbit pox viruses should be considered as vaccinia viruses, relying on a statement in document (1) that rabbit pox viruses are sufficiently closely related to vaccinia as to be regarded as a subspecies. The Appellant identifies both viruses as serologically related, having 86.9-97.1% identity at the DNA level and restriction patterns which are 60% homologous. The Board takes the view that although closely related, the viruses are not the same and, therefore, will start the analysis of novelty on the basis that the two viruses are different.

12. Document (1) describes a "marker rescue" experiment whereby cell monolayers are concomitantly infected with rabbit pox DNA fragments and vaccinia virus temperature sensitive mutants. The viral progeny is selected for at high temperature (40°C). Any vaccinia viruses capable of growing at that temperature must necessarily have been "rescued", that is they have had the temperature sensitivity defect of their parent repaired. The mechanism by which this "rescue" occurs is the replacement of the defective piece of vaccinia DNA by insertion into the vaccinia genome of the equivalent non-defective rabbit pox DNA restriction fragment by a recombinant process. Thus, taking into account that the defect must have been located in an essential region of

the genome, as a virus will not grow at high temperature, if it cannot perform an essential function at that temperature, document (1) shows the insertion of "foreign" rabbit pox DNA into an **essential** region of the vaccinia viral genome.

13. However, claim 1 requires the insertion of the foreign DNA fragment into a **non**-essential region of the genome. It is on this basis that the Board considers that document (1) does not destroy the novelty of the subject-matter of claim 1.

Inventive step (Article 56 EPC)

14. The Board agrees with the parties view that the closest prior art is document (2). It discloses that vaccinia virus exists in two forms, the L (large) and S (small) variants which may be distinguished by the size of their DNAs. Upon co-infection of sensitive CV-1 cells with the S variant and with **specific** restriction fragments carrying the DNA unique to the L variant, insertion of L variant-DNA into the S variant-genome is observed. Document (2) suggests that these results raise the possibility of utilizing pox viruses as vectors for foreign DNA.

15. The technical problem to be solved is making S variant vaccinia virus recombinant cloning or expression vectors.

16. The solution consists in a recombinant vaccinia virus which contains in a non-essential region of the genome a DNA segment which does not naturally occur in said virus, and which recombinant vaccinia virus has the properties specified in one of parts (a) to (c) of claim 1. The solution is arrived at in two steps, namely:

- flanking the foreign DNA to be ultimately carried by the vaccinia viral DNA with sequences derived from the non-essential regions of the viral genome,

- co-infecting sensitive cells with the molecule so obtained and an infective vaccinia virus.

17. Vaccinia viruses had already been used for approximately two hundred years for inoculation against smallpox. They were, thus, known as non-oncogenic viruses which could be expressed in mammals. Document (2) teaches that DNA can be recombined into them and suggests that they should be used as cloning vectors. In the Board's view, the skilled person would not have failed to appreciate the importance of these results, which implied that vaccinia viruses could become efficient and safe tools for introducing any DNA into mammals and obtaining expression thereof in mammals. Thus, it would have been obvious to try to find out if indeed vaccinia viruses could be made into cloning vectors.

18. The question to be asked with regard to inventive step is whether the skilled person would have reasonably expected that the project could be successfully brought to completion. In the Board's view, the skilled person on the basis of common knowledge available on vaccinia viruses, in particular, on the restriction patterns of the S and L variants (see document (11)) would have been aware that the L variant restriction fragments which could be recombined into the S variant genome were those which also carried at both extremities a substantial amount of DNA homologous to S variant-DNA, and would have concluded from Document (2) that for the L variant-DNA to be inserted into the S variant-genome, a recombination event had to take place between homologous portions of said DNA and genome.

19. Moreover, the skilled person considering this would also have taken into account document (1), which reports that ectromelia DNA may be inserted into the genome of the rabbit pox virus by a recombination process. Rabbit pox virus is known to be very similar to vaccinia virus, so that the skilled person would expect that a similar insertion of foreign DNA into the vaccinia viral genome should be possible. In document (1) two types of experiments are reported, of which the first related to rabbit pox whole genomic DNA and ectromelia viruses being co-infected into monolayers of sensitive cells. Ectromelia virus is unable to grow at 40°C, but it does produce haemagglutinin. Rabbit pox virus, on the other hand, grows at 40°C but does not produce haemagglutinin. The progeny coming out of the infection was selected for at 40°C. 3,3% of the viruses which grew at that temperature were positive in the haemadsorption test for haemagglutinin. According to the authors these viruses were recombinant rabbit pox viruses which had inserted in them and which expressed the ectromelia haemagglutinin gene.

20. During oral proceedings, the Respondents however submitted that as the experiment did not involve extensive purification of viral progeny, the possibility remained that the viral progeny was made of viral pseudotypes or of a mixture of rabbit pox and ectromelia viruses, i.e. of contaminants and not of genuine recombinant progeny. The Board cannot, of course, rule out that some contamination had taken place. However, the Board cannot, for the reasons given below, believe that readers would seriously believe that no recombination had taken place:

- It appears from reading document (1)(page 143:"..in a normal genome rescue experiment, there was some complementation of the coinfecting virus (data not

shown)"), that the authors were aware that the design of their experiment enabled some ectromelia viruses to grow. Yet despite this, the authors did not consider that the plaques observed at 40°C would be contaminants.

- The work has been published in a respected scientific journal, which implies that it had been reviewed by peer scientists who, it can be expected, would have refused publication, had they been of the opinion that no recombination had been observed or that there was sufficient doubt for further verification to be required.

- One of the authors of document (1) has provided the Board with a declaration (document (23)) in which the experiments of document (1) were discussed, which leaves the Board in no doubt that chimeric pox viruses could be formed by co-infecting whole cells with one type of poxvirus and naked DNA from another type of poxviruses.

- One of the inventors has in 1988 published an article (document (24)), in which it is stated that the work of documents (1) or (2) had opened the way to setting up a vaccinia virus cloning system. It must, thus, be that, at that point in time, the scientific community at large believed that document (1) did show recombination.

21. Furthermore, it is the Board's opinion that readers of document (1) would have understood from the fact that recombinant rabbit pox viruses formed plaques, that the haemagglutinin encoding DNA had been inserted into a non-essential region of the rabbit pox genome.

22. The second experiment disclosed the marker rescue of rabbit pox DNA restriction fragments in ectromelia viruses. It was found that only some of the rabbit pox DNA restriction fragments are marker rescued in the ectromelia viruses which, then, became capable of growth at 40°C. In the Board's view, these ectromelia viruses cannot have been contaminants precisely because they were only obtained in the marker rescue of certain specific rabbit pox DNA fragments. Indeed, if they were contaminants, they should equally have been found in all marker rescue experiments, independently of the nature of the restriction digests. Furthermore, the Board does not believe that the fact that some rabbit pox restriction digests did not enable the ectromelia viruses to grow at 40°C, should be considered as evidence that recombination cannot occur. It should rather be kept in mind that for growth at 40°C to occur, expression of the rescued rabbit pox markers is also needed. It, thus, may just be that in the rabbit pox DNA restriction enzyme digests which do not enable growth at 40°C, the region of DNA which is necessary for growth was destroyed by the restriction enzyme. If any conclusion can be drawn from this second experiment, it is that recombination is possible between ectromelia and rabbit pox DNA, which agrees well with the results of the first experiment that ectromelia DNA can be inserted into rabbit pox DNA by a recombination process.

23. The Board concludes that the experiments reported in document (1) would be taken by the skilled reader at face value.

24. Further the Respondents have argued that the existence of the two variant forms of vaccinia viruses (document (11)) would be taken as evidence that the vaccinia viral genome was inherently unstable and, therefore, unsuitable as vector DNA, so that in spite

of the teachings of document (1) and (2) the skilled person would have had a prejudice to the effect that it was not feasible to set up a cloning system with vaccinia viruses as vectors. In the Board's view, the existence of two vaccinia variants should rather be considered as an indication that DNA can be inserted into vaccinia with reasonable stability, because if the variant with a higher molecular weight were unstable, it could probably never have been isolated.

25. Document (2) thus provides the information that vaccinia viral DNA is capable of recombination with a DNA segment which is homologous to the vaccinia DNA in its extremities, and the suggestion that this raises the possibility of utilizing pox viruses as vectors for foreign DNA. Document (1) provides the information that foreign DNA is expressed when it is introduced into a non-essential region of the genomic DNA of a virus which is extremely close to vaccinia virus.

26. The skilled person starting from document (2) with the wish to solve the problem of making S variant vaccinia virus into recombinant cloning or expression vectors, would take into account document (1) relating to the very closely related rabbit pox viruses, and would derive from this the information with a reasonable expectation of success that vaccinia viruses are capable of recombination with a DNA segment which is homologous to the vaccinia DNA in its extremities, and that a vector made up of extremities homologous to vaccinia DNA and a cental part made up of foreign DNA should with a reasonable expectation of success allow this foreign DNA to be expressed in infected eukaryotic cells or host organisms and to encode an antigen or a biological product other than an antigen, that is to fulfil characteristic (b) of claim 1.

27. Characteristic (b) is the most broadly worded of the criteria (a), (b) or (c) stated in Claim 1 as properties that the recombinant vaccinia must have. The respondents have not alleged that any special measures need be taken to ensure the successful introduction or expression of foreign DNA in vaccinia virus by homologous recombination, nor is this apparent from the patent specification.

28. It would, thus, appear that, at the priority date, setting up a cloning system with vaccinia viruses as vectors would have been perceived as an endeavour likely to succeed and that isolating the recombinant vectors did not pose such problems as to prove that this assumption was wrong.

29. The Board is thus convinced that the skilled person at the priority date would have been able to arrive at a recombinant vaccinia virus characterized in that it contains in a non-essential region of the vaccinia genome a DNA segment which does not naturally occur in vaccinia viruses and which meet characteristic (b) of claim 1, and would have had a reasonable expectation of success in being able to do so. This means that Claim 1 of this request does not meet the requirements of Article 56 EPC, and it is not necessary, for this request, to consider whether the skilled person would also have a reasonable expectation of success for achieving characteristic (a) expression in a vaccinated mammal and of foreign DNA encoding an antigen which is capable of inducing an antibody-response or characteristic (c) the capacity of modifying, replacing or repairing defective genes in the infected eukaryotic cell or organism.

30. For the above reasons, the Board decides to reject the main request as not fulfilling the requirement of Article 56 EPC.

Auxiliary request I

31. Claim 1 differs from claim 1 of the main request in that the method of obtaining the claimed virus which is the subject-matter of granted claim 10 has been added as a further paragraph at the end of the claim, and the word "stably" has been inserted in the first line of the claim which, thus, reads: " A recombinant virus characterized in that it **stably** contains...", (emphasis added, see section X).

32. The method disclosed in claim 10 of the main request is the one used in the application as filed to isolate the claimed recombinant virus. The word "stably" does not appear as such in said application. The provided example shows, however, that the HA gene of influenza virus can be expressed from the vaccinia virus in cultured cells as well as in mammals. In the Board's view, these results imply that the insert must be stable. Furthermore, it is stated on page 9, lines 32 to 34 of the application as filed that other exogenous genes can similarly be introduced and expressed.

33. It is, thus, the Board's opinion that the amendments introduced into claim 1 do not result in the skilled person being presented with an information which is not directly and unambiguously derivable from the application as filed. Moreover, the amendments do not result in an extension of the subject-matter of the patent application. Accordingly, the auxiliary request fulfills the requirements of Article 123(2)(3) EPC.

34. In the Board's view, the word "stably" when used to define a DNA insertion has a definite although not necessarily quantitative meaning which is evident to the skilled person who will only be able to work with the recombinant virus if the inserted DNA remains in its place. It can, thus, be considered that the requirements of Article 84 EPC are fulfilled.

35. As for claim 1 of the main request no question as regards novelty arises.

36. The method of production of the recombinant virus by homologous recombination and the possibility that a prejudice existed in the art against viral stability have both been taken into account when assessing the inventive step of the main request. The reasoning developed in points 26 to 30, **supra** is, thus, equally valid for the claim 1 of this request. Accordingly, the same conclusion is reached that claim 1 of auxiliary request I does not fulfill the requirements of Article 56 EPC.

37. The Board decides to reject the auxiliary request I for lack of inventive step.

Auxiliary request II

38. Claim 1 of auxiliary request II differs from claim 1 of the main request by the insertion of the word "stably" in the first line of the claim and the addition of the expression "under vaccinia control" after the words "mammal", "host organisms" and " is" in parts (a), (b) and (c) respectively (see section XI, **supra**).

39. The origin of transcription of the herpes virus TK gene in the vaccinia virus recombinant is discussed on page 30 and 28 of application as filed. On page 32, the information is given that the HSV TK fragment is incorporated into the vaccinia virus in the cell and is then capable of replication and expression under vaccinia control. However, it is stated on page 28 where the experiment is described in more detail that a vaccinia virus promoter or the internal TK promoter could equally be responsible for the initiation of transcription of the TK gene. There is, thus, no unambiguous disclosure in the application as filed that the exemplified gene is expressed under vaccinia control. Nor is there any suggestion as to which specific control region should be used for the expression of other foreign genes.

40. The Board is of the opinion that the information that the foreign DNA segment should be expressed under vaccinia control is not directly and unambiguously derivable from the application as filed. The claim contains subject-matter which extends beyond the content of said application. The auxiliary request II is, thus, rejected as not fulfilling the requirements of Article 123(2) EPC.

Auxiliary request III

41. Claim 1 of this request is based on a combination of claims 1, 10 and 14 as granted, and directed to a vaccine comprising a recombinant vaccinia virus characterized in that it stably contains in a non-essential region of the vaccinia genome a DNA segment which does not naturally occur in vaccinia viruses limited to characteristic (a) of Claim 1 as granted,

and obtainable by the method of claim 10 as granted. The addition of the word "stably" here may be supported on the reasoning given in relation to Auxiliary request I above, and at first sight the requirements of Articles 123(2) and (3) EPC appear to be met.

42. The Board is thus prepared to allow the request into the proceedings, but the Board does not consider it appropriate to carry out the examination required under Article 102(3) EPC itself, but decides to use its powers under Article 111(1) EPC to remit the case to the Opposition Division for further prosecution. This will allow both the Respondents and the Appellants to direct their arguments on this request, in the knowledge of the reasoning on which the Board refused the other requests.

Order

for these reasons it is decided that:

1. The request to reject the appeal is refused.

2. The request to refer questions to the Enlarged Board of Appeal is refused.

3. The decision under appeal is set aside.

4. The matter is referred back to the first instance with the order for further consideration on the basis of the set of claims filed as the third auxiliary request at the oral proceedings on 18 April 1996.

The Registrar: The Chairwoman:

L. McGarry U. Kinkeldey