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D E C I S I O N
of 5 March 1997

Case Number: T 0187/93 - 3.3.4

Application Number: 84305909.8

Publication Number: 0139417

IPC: A61K 39/245

Language of the proceedings: EN

Title of invention:
Vaccines based on membrane bound proteins and process for making them

Patentee:
GENENTECH, INC.

Opponent:
Chiron Corporation

Headword:
Vaccines/GENENTECH

Relevant legal provisions:
EPC Art. 123, 83, 84, 54, 56

Keyword:
"Main, first and second auxiliary requests - sufficiency of disclosure and support by the description (no)"
"Third auxiliary request - added matter (yes)"
"Fourth auxiliary request - sufficiency of disclosure - support by the description (yes)"
"Novelty (yes)"
"Inventive step (yes) no reasonable expectation of success"

Decisions cited:
T 0612/92, T 0694/92, T 0296/93, T 0089/84, G 0006/95

Catchword:
(follows)

Catchword:
If a given technical effect (here: immunoprotection in vivo) is solely relied upon in order to demonstrate that a claimed subject-matter (here: a vaccine against a viral pathogen and its production method) involves an inventive step, claims of a broad scope are not allowable under Articles 83 and 84 EPC when, on the basis of the disclosure in the European patent application or the European patent and of the common general knowledge at the date of filing or at the priority date, said technical effect cannot be achieved by the skilled person without undue burden within the whole range of application claimed (cf. points 2 to 7 of the Reasons).

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Case Number: T 0187/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 5 March 1997

Appellant: (Opponent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 23 December 1992 concerning maintenance of European patent No. 0 139 417 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: R. E. Gramaglia
W. Moser

Summary of Facts and Submissions

I. European patent No. 0 139 417 based on application No. 84 305 909.8 was granted on the basis of claims 1 to 12. Its earliest priority date was 30 August 1983. Claim 1 read as follows:

"1. A process which comprises producing a truncated, membrane-free derivative of a membrane-bound polypeptide, said derivative being devoid of membrane-binding domain whereby the derivative polypeptide is free of said membrane, and having exposed antigenic determinants capable of raising neutralizing antibodies against a pathogen, said method comprising expressing DNA encoding said derivative in a stable eukaryotic cell line transfected with said DNA."

Claims 2 to 9 related to specific embodiments of the process of claim 1.

Claims 10 and 11 read as follows:

"10. A vaccine comprising a truncated, membrane-free derivative of a membrane-bound polypeptide, said derivative being devoid of membrane-binding domain whereby the derivative polypeptide is free of said membrane and having exposed antigenic determinants capable of raising neutralizing antibodies against a pathogen, the truncated polypeptide being a derivative of a glycoprotein D of the herpes simplex virus type 1 or type 2, and the pathogen is herpes simplex virus type 1 and/or type 2."

"11. A vaccine comprising a truncated, membrane-free derivative of a membrane-bound polypeptide, said derivative being devoid of membrane-binding domain whereby the derivative polypeptide is free of said

membrane and having exposed antigenic determinants capable of raising neutralizing antibodies against a pathogen, the truncated polypeptide being a derivative of a glycoprotein C of the herpes simplex virus type 1 or type 2, and the pathogen is herpes simplex virus type 1 and/or type 2."

Claim 12 related to a specific embodiment of the vaccine of claim 10.

II. An opposition was filed on the grounds of Articles 100(a) and 100(b) EPC, i.e., lack of novelty, lack of inventive step and insufficiency of disclosure. On 23 December 1992 the opposition division issued an interlocutory decision within the meaning of Article 106(3) EPC whereby the European Patent was maintained on the basis of claims 1 to 12 filed at the oral proceedings on 22 September 1992, which were considered to satisfy the requirements of the EPC.

Claims 1, 10 and 11 read as follows:

"1. A process which comprises producing a truncated, membrane-free derivative of a membrane-bound viral polypeptide, said derivative being devoid of membrane-binding domain whereby the derivative polypeptide is free of said membrane, and having exposed antigenic determinants that raise neutralizing antibodies and provides protection in an immunised subject against in vivo challenge by a viral pathogen, said method comprising expressing DNA encoding said derivative in a stable eukaryotic cell line transfected with said DNA."

"10. A vaccine comprising a glycosylated truncated, membrane-free derivative of a membrane-bound viral polypeptide, said derivative being the product of expression in, and secretion from, a eukaryotic host

cell of recombinant DNA encoding said viral polypeptide but lacking the membrane-binding domain whereby the derivative polypeptide is an immunogenic recombinant secretion product free of said membrane and having exposed antigenic determinants that raise neutralizing antibodies and provide protection in an immunised subject against in vivo challenge by a viral pathogen, the truncated polypeptide being a derivative of a glycoprotein D of the herpes simplex virus type 1 or 2, and the pathogen is herpes simplex virus type 1 and/or type 2."

"11. A vaccine comprising a glycosylated truncated, membrane-free derivative of a membrane-bound polypeptide, said derivative being the product of expression in, and secretion from, a eukaryotic host cell of recombinant DNA encoding said viral polypeptide but lacking the membrane-binding domain whereby the derivative polypeptide is an immunogenic secretion product free of said membrane and having exposed antigenic determinants that raise neutralizing antibodies and provide protection in an immunised subject against in vivo challenge by a viral pathogen, wherein the truncated polypeptide is a derivative of a glycoprotein C of the herpes simplex virus type 1 or type 2, and the pathogen is herpes simplex virus type 1 and/or type 2."

Claims 2 to 9 and 12 were the same as the corresponding granted claims.

III. The following documents are referred to in the present decision (numbering as used by the opposition division):

(E) EP-A-0 101 655

(G) EP-A-0 133 063

(H) Gething *et al.*, Nature, Vol. 300, pages 598 to 603 (1982)

(I) Sveda *et al.*, Cell, Vol. 30, pages 649 to 656 (1982)

(J) Rose *et al.*, Cell, Vol. 30, pages 753 to 762 (1982)

(L) Cohen *et al.*, Eight International Herpesvirus Workshop, Oxford, Abstract, page 268 (31 July to 5 August 1983)

(O) Wiley *et al.*, Nature, Vol. 289, pages 373 to 378 (1981)

(P) Wills *et al.*, J. Cellular Biochemistry, Vol. 23, pages 81 to 94 (1983)

(Q) Watson *et al.*, Science, Vol. 218, pages 381 to 384 (1982)

(W) Weis *et al.*, Nature, Vol. 302, pages 72 to 74 (3 March 1983)

(X) Bittle *et al.*, Nature, Vol. 298, pages 30 to 33 (1982)

(Y) Gerin *et al.*, Proc. Natl. Acad. Sci. USA, Vol. 80, pages 2365 to 2369 (April 1983)

(A1) Zoler *et al.*, Bio/Technology, pages 146 to 147 (April 1983)

(A2) Spear in "Cell Membranes and Viral Envelopes", H.A. Blough and J.M. Tiffany eds., Academic Press Inc., London, Vol. 2, pages 709 to 750 (1980)

(A3) Balachandran *et al.*, Infection and Immunity, Vol. 37, pages 1132 to 1137 (1982)

(A4) Dix *et al.*, Infection and Immunity, Vol. 34, pages 192 to 199 (1981)

(A5) Gething *et al.*, Proceedings of the First Meeting on Modern Approaches to Vaccines held in September 1983 at Cold Spring Harbor Laboratory, pages 263 to 268 (1984)

(A10) Mertz *et al.*, Journal of Infectious Diseases, Vol. 161, pages 653 to 660 (1990)

(A11) Chan w.L., Immunology, Vol. 49, pages 343 to 352 (June 1983)

(A12) Rachel *et al.*, Journal of Immunology, Vol. 130, pages 1413 to 1418 (March 1983)

(A15) Wilson *et al.*, Nature, Vol. 289, pages 366 to 373 (1981)

(A16) Brand *et al.*, Nature New Biology, Vol. 238, pages 145 to 147 (1972)

(A17) Kleid *et al.*, Science, Vol. 214, pages 1125 to 1129 (1981)

IV. The appellants (opponents) lodged an appeal against this decision. The respondents (patentees) filed counterarguments.

V. In a communication accompanying the summons to oral proceedings, the Board expressed its provisional view that the respondents' arguments in support of the inventive step (Article 56 EPC) might be in conflict with those submitted in favour of a broad claim 1 of the patent in suit as maintained by the opposition division, directed to a process for making a vaccine comprising a truncated glycoprotein from **any** viral pathogen (Articles 84 and 83 EPC), since the skilled person could apparently not predict with certainty whether the truncation of glycoproteins from a virus different from the exemplified Herpes simplex virus HSV might have deleteriously affected the conformation of the secreted viral glycoprotein in such a way as to destroy the epitopes responsible for immunoprotection *in vivo*. In response to this communication the respondents submitted on 5 February 1997 three subsidiary claim requests.

VI. At the oral proceedings held on 5 March 1997, the respondents submitted a further subsidiary claim request as second auxiliary request, the previous subsidiary requests 2nd to 3rd being renumbered as 3rd and 4th auxiliary requests, respectively.

VII. The claims of the **main request** correspond to the claims of the patent in suit as maintained by the opposition division (see Section II *supra*). The relevant claims of the auxiliary requests, showing in bold-type characters the amendments made in respect of the corresponding claim of the main request and in square brackets the deletions, are listed below.

Claim 1 of the **first auxiliary request** (claims 1 to 12) reads as follows:

"1. A process which comprises producing a truncated, membrane-free derivative of a membrane-bound **Herpes** viral polypeptide, said derivative being devoid of membrane-binding domain whereby the derivative polypeptide is free of said membrane, and having exposed antigenic determinants that raise neutralizing antibodies and provides protection in an immunised subject against in vivo challenge by a [viral pathogen] **Herpes virus**, said method comprising expressing DNA encoding said derivative in a stable eukaryotic cell line transfected with said DNA."

Claim 1 of the **second auxiliary request** (claims 1 to 12) reads as follows:

"1. A process which comprises producing a truncated, membrane-free derivative of a membrane-bound **Herpes simplex** viral polypeptide, said derivative being devoid of membrane-binding domain whereby the derivative polypeptide is free of said membrane, and having exposed antigenic determinants that raise neutralizing antibodies and provides protection in an immunised subject against in vivo challenge by a [viral pathogen] **Herpes simplex virus**, said method comprising expressing DNA encoding said derivative in a stable eukaryotic cell line transfected with said DNA."

Claim 1 of the **third auxiliary request** (claims 1 to 10) reads as follows:

"1. A process which comprises producing a truncated, membrane-free derivative of a [membrane-bound viral polypeptide] **Herpes virus glycoprotein D**, said derivative being devoid of membrane-binding domain

whereby the derivative polypeptide is free of said membrane, and having exposed antigenic determinants that raise neutralizing antibodies and provides protection in an immunised subject against in vivo challenge by a [viral pathogen] **Herpes virus**, said method comprising expressing DNA encoding said derivative in a stable eukaryotic cell line transfected with said DNA."

Claim 1 of the **fourth auxiliary request** (claims 1 to 9) reads as follows:

"1. A process which comprises producing a truncated, membrane-free derivative of [a membrane-bound viral polypeptide] **glycoprotein D of Herpes simplex virus type 1 or type 2**, said derivative being devoid of membrane-binding domain whereby the derivative polypeptide is free of said membrane, and having exposed antigenic determinants that raise neutralizing antibodies and provides protection in an immunised subject against in vivo challenge by [a viral pathogen] **Herpes simplex virus type 1 and/or type 2**, said method comprising expressing DNA encoding said derivative in a stable eukaryotic cell line transfected with said DNA."

Claims 2 to 5, 6 to 8 and 9 of this request are identical, respectively, to claims 2 to 5, 8 to 10 and 12 of the main request, exception made for renumbering and dependencies, where necessary.

VIII. The appellants submitted substantially the following arguments:

Sufficiency of disclosure and support by the description (Articles 83 and 84 EPC)

- Claim 1 of the main request was directed to a process for producing any viral glycoprotein from any virus. In the auxiliary requests, claim 1 was directed to a process for producing a polypeptide derivative of either any Herpes virus polypeptide or any Herpes simplex virus polypeptide or any Herpes virus gD protein or any Herpes simplex virus gD protein. However, the patent in suit failed to provide any guideline as to which immunogen was likely to confer immunoprotection *in vivo*. In the context of Herpes simplex membrane glycoproteins designed as gD of which only gD-1 had been exemplified, there was no proof that gD-2 was immunoprotective *in vivo*. HSV1 and HSV2 gD proteins were only 80% homologous (see page 6, lines 30 to 31 of the patent in suit). As for glycoproteins designed as gC, gA/B and gE of Herpes simplex virus, these had different biological functions and moreover, there was even less homology when compared with gD. Therefore no prediction could be made as to their immunoprotective action. In the ambit of glycoproteins of other Herpes viruses or of any other viruses, predictability as to their possible immunoprotective effect was even lower. For these reasons, claim 1 had to be restricted to the particular construct exemplified relating to gD-1.

Novelty (Article 54 EPC)

- Claim 8 of the fourth auxiliary request was not novel over document (E), a conflicting document under Article 54(3) EPC, disclosing the gD-1 expression plasmid pEH 4-2, in which 205 nucleotide (69 amino acids) of the 3'-terminus of

the gD-1 coding sequence had been deleted (see page 13, second paragraph). Upon expression of said plasmid, an immunoprotective vaccine was obtained (*ibidem*, page 82, Table 5). The teaching of document (E) was not limited to the exemplified *E. coli* as an expression system but also encompassed eucaryotic cells (*ibidem*, page 21, line 22 and claim 13) which would have ensured glycosylation of the gD protein.

Inventive step (Article 56 EPC)

- The process of claim 1 of all requests was obvious in view of documents (A1) and (H) in combination with document (A11). Before the priority date of the patent in suit, sub-unit vaccines were well known and produced by a variety of techniques, including recombinant DNA techniques. It was known that the regions of a membrane-bound glycoprotein responsible for antigenicity were to be found in the extracellular domain (ectodomain). It was also known that in the case of viral membrane-bound glycoproteins, deletion of the transmembrane domain did not affect the antigenic properties of the ectodomain. This was shown by document (A1) and document (H) relating to the production of the influenza virus haemoagglutinin (HA) without the transmembrane domain. Document (H) showed that the "anchor-minus" variant of HA was glycosylated and assembled as trimer of HA subunits, as was native HA. The deletion of the transmembrane domain of the glycoprotein of vesicular stomatitis virus (VSV G) also led to a protein having the same immunogenicity as the native VSV G (see document (J)). Therefore, as regarded immunisation with either the whole native membrane protein including the transmembrane and intracellular domains *versus* immunisation with the ectodomain of that protein

only, it would have been the skilled person's expectation that removal of the transmembrane domain would not have had any effect on the immunogenicity of that portion of the protein that was extracellular. As regarded the isolated membrane glycoproteins of Herpes simplex virus (HSV) such as gD, these were known to be immunoprotective in vivo (see documents (A11) and (A12)). Thus, there was nothing surprising in finding out that the truncated form of gD elicited an immunoprotective response *in vivo*.

- The ability of an antigen to elicit *in vitro* neutralizing antibodies was a strong indicator that the antigen would be protective *in vivo*. The correlation between the ability of an antigen to elicit neutralizing antibodies and the ability of that antigen to protect an immunised host from *in vivo* virus challenge was reinforced in cases where successful passive protection with these neutralizing antibodies had been shown. This was because, in this case, cytotoxic T-cell response turned out not to be essential to protect the subject from attack. As regarded the membrane proteins of HSV, it was known that gD expressed as a truncated fusion protein in *E. coli* not only retained the antigenic determinants of the native gD protein (document Q) but also elicited neutralizing antibodies in animals (documents (Q) and (W)). It was also known from document (L) that a fragment of the extracelluar domain of gD-1 comprised a neutralizing epitope. In the case of HSV gD and gC, it had been demonstrated (see documents (A3) and (A4)) that neutralizing antibodies raised against these proteins were capable of passive protection. The person skilled in the art had therefore a reasonable expectation that the production of a known membrane-bound

glycoprotein by expressing a gene encoding the glycoprotein devoid of the transmembrane domain would have resulted in a product retaining its ability to protect an immunised subject *in vivo*. The appellants submitted declarations from Professor Enquist, Dr Gething, Professor Pereira, Professor Nossal and Professor Roitt in support of the above arguments.

IX. In support of the subject-matter of all their requests, the respondents argued essentially as follows:

Sufficiency of disclosure and support by the description (Articles 83 and 84 EPC)

- The discovery by the present inventors that a truncated, membrane-free derivative of gD of HSV conferred immunoprotection, gave rise to a reasonable expectation that the system would be successful with other pathogens. This expectation arose because the successful results produced in the HSV model demonstrated that all the technical problems leading to a successful vaccine had been overcome. These problems were that the truncated glycoprotein had to elicit neutralizing antibodies and confer immunoprotection *in vivo* and also generate the necessary cellular immune component.

Novelty (Article 54 EPC)

- The subject-matter of claim 8 of the fourth auxiliary request was identical with the subject matter of claim 10, which had been held allowable by the opposition division. During the appeal proceedings, the issue of lack of novelty of the subject-matter of this claim 8 (former claim 10) had not been raised by the appellants in their written submissions, neither had novelty of the

subject-matter of former claim 10 been an issue in the opposition proceedings. It was therefore legally inadmissible to raise this point for the first time during oral proceedings before the Board. If the Board nevertheless intended to consider this point, then the appeal proceedings had to be continued in writing in order to give the respondents sufficient time to submit counterarguments.

Inventive step (Article 56 EPC)

- The skilled person would have turned neither to the technique disclosed by document (A1) nor to glycoprotein D of Herpes simplex type 1 or type 2 because the former yielded less immunogenic monomers (see document (A1), page 147, l-h column, last full paragraph and document (A5), page 266, lines 3 to 4 from the bottom), while the latter had proven not to be immunogenic in soluble form (document (A12), page 1416, r-h column, last paragraph), i.e, the form achieved through the technique of document (A1).

- Viruses were complex mosaics of various components including glycoproteins, that were arranged conformationally in a specific way. There was a consensus among the skilled persons that this conformation was likewise required for antibody recognition and protection *in vivo* since the antigen had to be appropriately presented to mediate an immune response in the immunised host. Before August 1983, the skilled person could not have reasonably predicted that a vaccine based solely on the truncated glycoprotein that was not associated with its membrane domain, would have exhibited the same conformation as in the virus and hence the property of immunoprotection *in*

vivo. There was indeed no proven case of *in vivo* protection afforded against a pathogen based solely on the truncated, membrane-free derivative of a membrane glycoprotein. Documents (H), (I) and (J) merely related to the secretion of membrane bound proteins but said nothing as to whether the secreted proteins were able to immunoprotect a host from the virus challenge. The situation depicted in document (Q) was in no way comparable with that of a truncated protein secreted by a mammalian cell since it dealt with the expression in *E. coli* of unglycosylated gD fused to a β-galactosidase protein. As to the appellants' argument that the ability of an antigen to elicit *in vitro* neutralizing antibodies was an indicator that the antigen would most likely elicit an immunoprotective response *in vivo*, it was true that neutralizing antibodies added in a sufficient quantity to an *in vitro* cell system inhibited virus infection that could be quantified in various ways. However, this *in vitro* neutralizing activity was not predictive of *in vivo* protection. Raising neutralizing antibodies might be required for *in vivo* immunoprotection but it was certainly not itself sufficient. Many instances were known in which a high number of neutralizing antibodies were raised, yet these failed to protect the host from pathogenesis. The role of the T-cell response was also not elucidated yet but the scientific community did not exclude that cellular immunity was also important to immunoprotection *in vivo*. Thus, an immunogen that elicited "neutralizing antibodies" did not suggest any benefit *in vivo* in terms of protection against infection by the virus or prevention of spread of the virus. The respondents submitted the declarations of Professor Rose and Dr. Skehel in support of the above arguments.

X. The appellants requested that the decision under appeal be set aside and that European patent No. 139 417 be revoked.

The respondents requested that the appeal be dismissed or that the patent be maintained on the basis of one of the following auxiliary requests:

(a) First auxiliary request: claims 1 to 12 filed on 5 February 1997 as first subsidiary claim request.

(b) Second auxiliary request: claims 1 to 12 submitted during oral proceedings.

(c) Third auxiliary request: claims 1 to 10 filed on 5 February 1997 as second subsidiary claim request.

(d) Fourth auxiliary request: claims 1 to 9 filed on 5 February 1997 as third subsidiary claim request.

Reasons for the Decision

Main request
Article 123(2) and (3) EPC
Claims 1, 10 and 11

1. Claims 1, 10 and 11 had been amended at the opposition stage. No objections under Article 123(2) and (3) EPC have been raised by the appellants in respect of these

claims and the Board also sees none. In fact, claim 1 differs from claim 1 as granted by the expression "and provides protection in an immunized subject against in vivo challenge by a viral pathogen" which finds a basis on page 4, last line, page 21, lines 23 to 25, pages 28 to 29 (under the heading "Virus challenge") and on page 48, first paragraph of the application as filed. The qualification of the polypeptide as "viral" in claims 1 and 10 is also supported by the original disclosure (see eg., pages 4 to 6). The addition of the term "glycosylated" in claims 10 and 11 finds its counterpart on page 15, lines 20 to 25 and page 48, line 6 of the application as filed. Further, the above amendments also amount to a restriction of the protection conferred by the corresponding granted claims. Therefore, the claims of the main request fulfil the requirements of Article 123(2) and (3) EPC.

Sufficiency of disclosure (Article 83 EPC) and support for the claims in the description (Article 84 EPC)
Claim 1

2. Claim 1 as granted comprised the essential technical feature that the truncated polypeptide produced by the method claimed should have exposed antigenic determinants "capable of raising **neutralizing antibodies** against a pathogen" (see section I *supra*). During the opposition procedure, said technical feature has become "capable of **raising neutralizing antibodies and provides protection in an immunised subject against in vivo challenge by a viral pathogen**" (see section II *supra*). In the context of the discussion on inventive step, the respondents argued that this additional technical effect, namely immunoprotection against an *in vivo* challenge by a virus, was an exceptional one that went many steps beyond the mere induction of neutralizing antibodies. The Board agrees that

conferring immunoprotection by an immunogen is a far more demanding task than merely eliciting neutralizing antibodies (see point 30 *infra*). In view of this, whether this technical effect can be arrived at without undue burden by the skilled person **within the whole range** of viral polypeptides of claim 1, becomes a relevant question.

3. The respondents argued that before August 1983, i.e., the earliest priority date of the patent in suit, the skilled person could not have reasonably predicted that a vaccine based solely on the truncated viral glycoprotein that was not associated with its membrane domain, would have exhibited the property of immunoprotection *in vivo*. This advantageous property was intimately linked with the conformation of the secreted truncated protein and with the host's T-cell response. These two aspects were not yet elucidated before the earliest priority date of the patent in suit and thus the skilled person could not predict in advance their role upon immunoprotection *in vivo*. In particular, the antigenic presentation was far from simple. In some cases the membrane glycoprotein was incorporated in the membrane as monomer, while in other cases it was found as oligomer. The primary, secondary, tertiary and quaternary structure of the membrane glycoprotein offered a considerable scope for variation in antigenicity and hence immunogenicity. It was not known whether a truncated membrane glycoprotein would have folded properly in order to exhibit a (native) conformation exposing epitopic determinants necessary for eliciting neutralizing antibodies and immunoprotection *in vivo*. As regards a possible host's

T-cell response, Professor Rose, a respondents' expert (see his Declaration dated 20 December 1993, item 10) emphasized that for many viral pathogens the role of T-cell response for having immunoprotection *in vivo*, was not known in view of the fact that each virus has a different pathogenesis *in vivo*.

4. As it will be seen below in the discussion of inventive step of the subject-matter of claims 1 and 8 according to the fourth auxiliary request (see point 28 *infra*), the Board agrees that it was not known to the skilled person whether the truncated membrane glycoprotein gD from HSV would have folded properly in order to exhibit a (native) conformation exposing epitopic determinants necessary for eliciting neutralizing antibodies and immunoprotection *in vivo* in view of the considerable scope for variation in immunogenicity provided by the primary, secondary, tertiary and quaternary structure, not to mention the role of the T-cell response which was likewise unknown to the skilled person.

5. However, since slight changes in the three-dimensional conformation may have unpredictable effects in the host's immune response (see point 28 *infra*), the Board is, for the sake of consistency, also entitled to conclude that the skilled person **must** experience the same uncertainty in relation to any other truncated membrane-bound polypeptide from **any virus,** having no amino acid homology with gD from HSV. This is because no two membrane glycoproteins from unrelated viruses are the same. A comparison between Figure 5B on page 94 of document (P) with Figure 2 on page 368 of document (A15), relating to glycoproteins from the Rous sarcoma virus and influenza virus, respectively, shows this. Further, there is no common technical feature automatically turning up as a result of the truncation process, which common feature is of necessity capable

of producing or preserving the epitope(s) responsible for *in vivo* immunoprotection, said feature being valid for **any** membrane glycoprotein from **any** virus. Thus, the skilled person cannot predict with certainty whether the truncation of glycoproteins from a virus different from the exemplified gD from HSV might deleteriously affect the conformation of the secreted viral glycoprotein in such a way as to destroy the epitopes responsible for immunoprotection *in vivo*. As a consequence, the results relating to gD from HSV **cannot** be extrapolated to glycoproteins from the whole range of all other viruses. Thus, it can reasonably be expected that the skilled person, when trying to obtain the same technical effect with a glycoprotein from a viral pathogen different from HSV, would experience the same lack of predictability as in the case of gD from HSV, which uncertainty may thus lead to undue burden and/or possible failures (Article 83 EPC).

6. In two recent decisions, namely T 612/92 of 28 February 1996 and T 694/92 of 8 May 1996 (to be published in the OJ EPO), which dealt with cases in the area of recombinant DNA technology, the competent Boards were confronted with a situation in which, like in the present case, the technical information in the description of the patent specification was held to be insufficient to allow the invention to be carried out over the whole range of the claimed application. It was thus decided in both cases that under such technical circumstances, claims of broad scope could not be allowed.

7. The present case like the case of decision T 694/92 (*supra*, see in particular points 14 to 15) is one in which the respondents' arguments in support of a broad claim 1 (Articles 83 and 84 EPC) conflict with those submitted in favour of the inventive step (Article 56

EPC). For the reasons given above, the Board comes to the conclusion that a broad claim 1 directed to producing a truncated, membrane-free derivative of **any** membrane-bound viral polypeptide from **any** virus having the property of raising neutralizing antibodies and providing protection in an immunized subject against *in vivo* challenge by **any** viral pathogen, **is not compatible** with the Board's acceptance of the respondent's arguments in support of Article 56. In fact, the experimental evidence and technical details in the description of the patent in suit are found by the Board not to be sufficient for the skilled person to reliably achieve without undue burden the technical effect looked for of obtaining an *in vivo* immunoprotective vaccine within the whole range of application claimed.

Claim 1 thus does not fulfil the requirements of Articles 83 and 84 EPC and the main request, of which claim 1 is part, is consequently refused.

First auxiliary request
Article 123(2) and (3) EPC
Claim 1

8. Claim 1 of this request differs from claim 1 of the main request by the expression "Herpes viral polypeptide" instead of "viral polypeptide" and by "Herpes virus" instead of "viral pathogen", which amounts to a restriction of the membrane-bound viral polypeptides and of the viral pathogen recited in claim 1 of the main request to those of the Herpes virus family. A basis for this amendment is to be found on page 6, line 21 of the application as filed, wherein it is stated "This invention is particularly directed to the exploitation of those membrane-bound polypeptides associated with pathogenic organisms,

e.g., herpes virus". Although the whole application is essentially concerned with Herpes simplex viruses (HSV), the Board interprets the expression "herpes virus" in this passage as relating to the broad family of Herpes viruses, in the sense, e.g., of page 711 (see Table I) of document (A2). "Herpes virus" is in fact a sub-family of the "pathogenic organisms" referred to previously in the same sentence. Further, the above amendments also amount to a restriction of the protection conferred in comparison with the corresponding claim as granted.

Therefore, the claims of the first auxiliary request fulfil the requirements of Article 123(2) and (3) EPC.

Sufficiency of disclosure (Article 83 EPC) and support for the claims in the description (Article 84 EPC)
Claim 1

9. In claim 1 of this request, a restriction of the membrane-bound viral polypeptides to those from the Herpes virus family (see point 8 *supra*) has been effected. However, according to document (A2) (see page 730, line 1 to 10 from the bottom) there have been no reports of cross-neutralization between any pairs of the human herpesviruses (HSV, cytomegalovirus, varicella-zoster virus and the Epstein-Barr virus) and the DNAs of HSV virus and of Epstein-Barr virus share few, if any, sequences in common. Thus, the glycoproteins from viruses of the Herpes family are as unrelated as glycoproteins of viruses from different families. This view is further confirmed by document (A2) (see page 710, lines 4 to 5 from the bottom) stating that many Herpes viruses have been classified as herpesviruses solely on morphological criteria.

Consequently, the same conclusions arrived at by the Board in points 4 to 7 *supra* must apply to claim 1 of this request that the claim does not fulfil the requirements of Articles 83 and 84 EPC. Consequently, this request, of which claim 1 is part, is also refused.

Second auxiliary request
Article 123(2) and (3) EPC
Claim 1

10. Claim 1 of this request differs from claim 1 of the main request by the expression "Herpes simplex viral polypeptide" instead of "viral polypeptide" and of "Herpes simplex virus" instead of "viral pathogen". A basis for this amendment is to be found on page 5, second paragraph and in claim 6 of the application as filed. Further, the above amendments also amount to a restriction of the protection conferred by the corresponding granted claim. Therefore, the claims of the second auxiliary request fulfil the requirements of Article 123(2) and (3) EPC.

Sufficiency of disclosure (Article 83 EPC) and support for the claims in the description (Article 84 EPC)
Claim 1

11. In claim 1 of this request, a restriction of the membrane-bound viral polypeptides to those from the Herpes simplex virus family (see point 10 *supra*) has been effected. However, glycoproteins gD, gC, gA/B and gE of Herpes simplex virus possess less than 10% amino acid homology and are thus antigenically distinct (see e.g., document (Q), page 381, left-hand column, lines 17 to 18 from the bottom). Moreover, these glycoproteins exert a different biological function in the process of infection. Glycoprotein gB is known to mediate fusion between the viral and cellular membrane

(see document (G), page 2, lines 1 to 3), while glycoprotein gC is known not to be essential for virion penetration (see document (A2), page 728, lines 8 to 11). The biological function of glycoprotein gE is associated with Fc-binding activity (*ibidem*, page 740, line 8). In conclusion, glycoproteins gA/B, gC, gD and gE from Herpes simplex virus are as unrelated as glycoproteins of viruses from different families.

Consequently, the same conclusions arrived at by the Board in point 4 to 7 *supra* must apply to claim 1 of this request, namely that this claim does not fulfil the requirements of Articles 83 and 84 EPC. Consequently, this request, of which claim 1 is part, is also refused.

Third auxiliary request
Article 123(2) EPC
Claim 1

12. Claim 1 of this request differs from claim 1 of the main request by the expression "Herpes virus glycoprotein D" instead of "membrane-bound viral polypeptide" and of "Herpes virus" instead of "viral pathogen". These changes amount to a delimitation of the membrane-bound viral polypeptides to the glycoproteins D of any Herpes virus. However, a basis for this amendment cannot be found in the application as filed, in which the terms "glycoprotein D", "glycoprotein D-1" or "glycoprotein D-2" are always associated with the terms "HSV", "HSV1" or "HSV2", respectively, but never with the wording "Herpes virus" as a broader family. This finding is consistent with document (A2), a detailed treatise on Herpes viruses, wherein the verbal association "glycoprotein D of Herpes virus" can also not be found and thus no glycoproteins D of e.g., Epstein-Barr virus or Varicella-zoster virus (other viruses of the Herpes

family) are mentioned. Therefore, claim 1 relates to subject-matter which is neither explicitly nor implicity derived from the application as filed and for this reason offends against the requirements of Article 123(2) EPC. This request, of which claim 1 is part, is consequently also refused.

Fourth auxiliary request
Articles 123(2) and (3) EPC
Claim 1

13. Compared with claim 1 of the main request, claim 1 of this request differs by the expression "glycoprotein D of Herpes simplex virus type 1 or type 2" instead of "a membrane-bound viral polypeptide" and of "Herpes simplex virus type 1 and/or 2" instead of "a viral pathogen". This is a delimitation of the membrane-bound viral polypeptides to the glycoproteins D of Herpes simplex virus type 1 or type 2. A basis for this amendment is to be found on page 5, second paragraph and in claim 6 of the application as filed. Further, the above amendments also amount to a restriction of the protection conferred by the corresponding granted claim. Therefore, the claims of the fourth auxiliary request fulfil the requirements of Article 123(2) and (3) EPC.

Sufficiency of disclosure (Article 83 EPC) and support for the claims in the description (Article 84 EPC)
Claim 1

14. In claim 1 of this request, a restriction of the membrane-bound viral polypeptides to glycoproteins gD of Herpes simplex virus (see point 13 *supra*) has been made. These are gD-1 and gD-2. The appellants point out that there is no proof in the patent in suit that gD-2 is immunoprotective *in vivo* and argue that the immunoprotective properties of gD-1 shown in the patent

in suit cannot be extrapolated to gD-2 in view of the only 80% amino acid homology between the exemplified gD-1 and gD-2 (see page 6, lines 30-31 of the patent in suit) and also because gD-1 and gD-2 merely exhibit type-specific rather than type-common epitopes. However, the Board disagrees with this position for the reasons given hereinafter. It is true that two proteins with 80 % amino acid homology are not of necessity structurally similar from the viewpoint of the primary, secondary, tertiary and quaternary conformation. However, as far as gD-1 and gD-2 are concerned, the Board observes that not only document (Q) (see page 381, left-hand column, lines 5 to 9 from the bottom) demonstrates that gD-1 and gD-2 share type-common epitopes, but Example 1 on pages 13 to 14 of the patent in suit (see the chapter headed "HSV-2 virus challenge") shows that mice immunized with truncated gD-1 are immunoprotected against an *in vivo* challenge not only with HSV-1 but **also with HSV-2**. Hence, it can be concluded that the immune response elicited by truncated gD-1 somehow fails to "distinguish" between gD-1 and gD-2 exposed on the surfaces of HSV-1 and HSV-2, respectively. Such an immune response can only be expected in the case of a very high structural similarity between gD-1 and gD-2.

Thus, unlike the cases dealt with in points 4 to 7, 9 and 11 *supra*, wherein a structural similarity between the exemplified gD-1 and the other viral glycoproteins recited in claim 1 could not been found, the Board is inclined to acknowledge a close structural similarity between gD-1 and gD-2 of Herpes simplex virus type 1 and type 2. Consequently, given the fact that a truncated, membrane-free derivative of gD-1 of HSV-1 confers *in vivo* immunoprotection, it is plausible that the claimed invention can be put into practice successfully without undue burden or inventive skill

also with truncated gD-2 of HSV-2. This is in view of the close structural similarity between gD-1 and gD-2 (cf. an analogous technical situation in the case of decision T 694/92, *supra*, in particular points 25-26 of the Reasons).

Therefore, in the Board's judgment, claim 1 of the fourth auxiliary request satisfies the requirements of Articles 83 and 84 EPC.

Novelty
Claim 8

15. As regards the procedural question of whether or not the issue of lack of novelty of the subject-matter of claim 8 (former claim 10) could be raised during oral proceedings notwithstanding the fact that this issue had not been raised by the appellants in their written submissions (see section IX *supra*), the following has to be taken into consideration: Contrary to the respondents' assertion, novelty of the subject-matter of claim 8 (then claim 10) was an issue in the opposition proceedings (see points 4.2.1 and 4.2.2 of the Reasons of the decision under appeal). According to an established jurisprudence, the Board could reopen any matter which has been decided by the opposition division without the matter being raised by the appellants (see T 89/84, OJ EPO 1984, 562, point 5 of the Reasons). On the other hand, given the fact that Rule 71a(1) EPC is **not** applicable to the Boards of Appeal (see G 6/95, OJ EPO 1996, 649), the Board was not obliged to draw attention to the above-mentioned issue when issuing the summons for oral proceedings. From these considerations it follows therefore that the

respondents' submission, according to which it was legally inadmissible to raise the novelty issue in respect to the subject-matter of claim 8, is not correct.

Since the Board, for the reasons given hereinafter under point 16, is satisfied that the subject-matter of claim 8 is novel, considerations of whether or not the appeal proceedings should be continued in writing (see section IX *supra*) could be dispensed with.

16. The appellants questioned the novelty of claim 8 under Article 54(3),(4) EPC having regard to document (E) (see section VIII *supra*). The Board agrees that the teaching of document (E) is not limited to the exemplified *E. coli* as an expression system but also encompasses eucaryotic cells (see page 21, line 22 and claim 13) which would ensure glycosylation of the gD protein. However, even by assuming that the fusion protein disclosed by document (E) were a "glycosylated truncated, membrane-free derivative of a glycoprotein D of a herpes simplex virus type 1 or 2" as recited in the contested claim 8, the additional feature in claim 8 "having exposed antigenic determinants that provide protection in an immunised subject against in vivo challenge by a viral pathogen" **cannot** be deduced from document (E). In fact, Table 5 on page 82 of this document merely relates to the immunoprotective effect of the unglycosylated fusion protein preparation from pEH 4-2, made in *E.coli* (see page 53, lines 12 to 13).

The appellants maintain that, should the skilled person put into practice the teachings of document (E) and turn to a eucaryotic cell as an expression vector, the resulting glycosylated fusion protein would automatically acquire the property of conferring immunoprotection to a host against *in vivo* challenge

with a virus. However, in the absence of any evidence showing this, either from the appellants or from later literature, the Board cannot follow this unsubstantiated assumption by the appellants. Consequently, the subject-matter of claim 8 is considered to be novel within the meaning of Article 54 EPC. The remaining claims 1 to 7 and 9 have not been challenged from the viewpoint of the novelty and the Board does not see any valid ground for doing so of its own motion. Novelty is therefore acknowledged.

Inventive step (Article 56 EPC)
Claims 1 and 8
Closest prior art

17. Document (A1) represents the closest prior art for the claims at issue. This document is a report on the technique for converting virus proteins that are normally anchored in the membrane of eucaryotic cells infected by the virus, into proteins that are secreted by the infected eucaryotic cells. The said technique relies on the expression in eucaryotic cells of a DNA sequence coding for the viral protein, in which the sequence coding for the hydrophobic anchor (i.e., the transmembrane domain) of the viral membrane protein has been deleted. Thereby, as reported, vast quantities of material could be produced and easily purified. As examples of said anchor-minus mutants, reference is made in this scientific report to previous works published as documents (H) and (J) relating to the construction of mutants devoid of the transmembrane domain of the hemagglutinin (HA) of influenza virus and of the G protein of vesicular stomatitis virus (VSV G), respectively. A statement is also made in document (A1) that the truncation technique discussed therein could be useful in the production of viral antigens for subunit vaccines.

18. In the light of document (A1), the problem to be solved can be seen in the provision, by application of the same technology disclosed in this document, of viral antigens for subunit vaccines against the Herpes simplex virus type 1 and/or type 2.

19. The solution proposed by the patent in suit is the subject-matter of claims 1 to 9 at issue, namely a process by which a DNA encoding the truncated (anchor-minus) derivative of glycoprotein D of Herpes simplex virus type 1 or type 2 is expressed in a transfected eucaryotic cell, said derivative having exposed antigenic determinants that raise neutralizing antibodies and provide protection in an immunised subject against in vivo challenge by a Herpes simplex virus type 1 and/or type 2. In view of Example 1 of the patent in suit, in particular Tables 1, 2 and 3 thereof, the Board is satisfied that the above-stated technical problem has been solved since it has been shown that the anchor-minus glycoprotein D of Herpes simplex type 1 or type 2 is indeed capable of raising neutralizing antibodies and providing protection in an immunised subject against *in vivo* challenge by a Herpes simplex virus type 1 and/or type 2.

20. The relevant question in respect of inventive step is whether the skilled person would have applied the technique described in document (A1) to membrane glycoprotein D of Herpes simplex type 1 or type 2 and whether he or she would have reasonably expected that the recombinantly produced anchor-minus protein would have provided in an immunised subject immunoprotection against an *in vivo* challenge of Herpes simplex virus type 1 and/or type 2.

21. In this respect, attention is drawn to the statement in decision T 296/93 (OJ EPO 1995, 627) that "a reasonable expectation of success" should not be confused with the

skilled person's "hope to succeed" (see *loc. cit.* point 7.4.4 of the Reasons). In fact, even if an experiment is obvious to try for the skilled person, it is not necessarily true that this person would have any reasonable expectation of success when embarking on it.

22. The appellants submit that the HSV gD protein, the encoding sequence of which was fully known (cf. document (Q)), was the most obvious candidate for the application of the technique described in document (A1). The respondents maintain that in order to solve the technical problem the skilled person would not have turned to the technique disclosed by document (A1) nor would he or she have used glycoprotein D of Herpes simplex type 1 or type 2. Document (A1) dealt mainly with the production of proteins in soluble form in recombinant systems for the purpose of ease of purification. The technique used yielded monomers that were less immunogenic than the polymeric form thereof embedded in the membranes (see document (A1), page 147, 1-h column, last full paragraph). On the other hand, glycoprotein D had proven not to be immunogenic in soluble form (document (A12), page 1416, r-h column, last paragraph), i.e, the form achieved through the technique of document (A1)'.

23. In the Board's judgement, the skilled person faced with the underlying technical problem would have seriously taken into consideration the technical approach referred to in document (A1) for the production of soluble HSV gD protein. He or she knew from document (A11) (see Figure 5(c) on page 350 in combination with page 348, 1-h column: "each glycoprotein in saline") that soluble gD was immunoprotective and that monovalent, anchorless monomers could have easily been made polyvalent (and thus more immunogenic) by cross-linking (see document (A1), page 147, 1-h column, lines 13 to 15 from the bottom). However, the decisive

question here is whether, before August 1983, i.e., the earliest priority date of the patent in suit, the skilled person could have reasonably predicted that a vaccine based solely on the recombinantly produced, truncated viral glycoprotein D that was not associated with its membrane domain, would have exhibited the property of conferring immunoprotection *in vivo*.

24. In this respect, the Board's considerations are as follows:

At the earliest priority date of the patent in suit, there was a consensus among the scientific community, as reflected by the declarations of Professor Roitt (an appellants' expert) dated 31 January 1995 (see point 9) and of professor Rose (a respondents' expert) dated 20 December 1990 (see paragraphs 8 to 10), that both humoral immunity (neutralizing antibodies) and the host's T cell response (cell mediated immunity) were important for an immunogen to be capable of conferring to an immunised host immunoprotection against an *in vivo* challenge with a pathogen. Both humoral immunity and cell mediated immunity were believed to depend on the conformation of the immunogen. This correlation between the immunogenic properties of a molecule and its conformation is pointed out in many of the documents available to the Board, some of which are concerned with glycoprotein gD of Herpes simplex virus. For example:

- Document (O) purports to find an answer to the question "Which regions of the molecule are immunogenic and dominant in humoral and cellular immune recognition?" (see page 373, 1-h column).

- Document (Y), recites on page 2365, l-h column, lines 1 to 3: "...a number of studies have suggested that the immunogenicity of a protein molecule largely depends on its conformation".

- Document (A17), states on page 1128, last paragraph that: "In order to elicit the protective immunogenic response demonstrated in our study the biosynthetic LE'-VP3 antigen must present an immunogenic site as it appears in the intact virion."

- The failure by glycoprotein VP1 of foot-and-mouth disease virus (FMDV) to induce neutralizing antibodies is explained in document (X), page 33, r-h column, lines 1-4, by a possible conformation change: "It is possible that the separated VP1 does not fold properly when deprived of the scaffolding provided by the other capsid proteins. Thus the immunodominant site presented to the immune system by free VP1 may be largely irrelevant to neutralization".

The correlation immunogenicity/three-dimensional structure is also emphasized in the declarations submitted by the experts of both the respondents and the appellants. In Dr Skehel's declaration dated 19 December 1990, point 9, it is stated "... it is still not understood why some proteins will or will not fold into their native conformational structure so as to expose antigenic epitopes necessary for neutralizing (protective) activity". In Dr Nossal's declaration dated 30 January 1995, point 30, concern is expressed that antigenicity may be affected by the incorrect folding of the recombinant protein.

25. With a view to the T-cell response evoked by Herpes simplex virus or glycoprotein D thereof, it was common belief before the earliest priority date of the patent in suit, that this response was **actually** involved in immunoprotection (see document (A4), page 192, l-h column, lines 4 to 7, document (A11), page 351, r-h column, last paragraph, and document (A12), page 1413, l-h column, last two lines). However, the mechanism by which T- cell response to gD mediated immunoprotection, was not known even two months before the earliest priority date of the patent in suit (August 1983), (see document (A11) (ibidem), published June 1983). In fact, such uncertainty still persisted as late as 1990, and document (A10) shows this (see page 659, r-h column, first full paragraph).

26. In summary, the correlation host's immunoprotection/three-dimensional structure of the immunogen, which emerges from points 24 to 25 *supra*, reduces the problem of establishing whether the skilled person could have reasonably predicted that a vaccine based solely on the truncated viral glycoprotein not associated with its membrane domain, would have exhibited the capacity of conferring immunoprotection *in vivo*, to the simpler one of how much does truncation of a viral glycoprotein affect the secondary, tertiary and quaternary structure of the ectodomain.

27. In connection with this, it is argued by the appellants that deletion of the transmembrane domain of a membrane bound viral glycoprotein does not affect **at all** the conformation of the extracellular domain (ectodomain), the only portion of the molecule responsible for antigenicity. The appellants rely on documents (H), (J) and (A16) to buttress this view. The Board, however, observes that these documents are not concerned with *in vivo* immunoprotection. From document (H) (see Legend to

Figure 3 on page 601) it can merely be deduced that truncated HA reacts with anti-HA serum. Document (J) (see page 760, r-h column, last paragraph and page 758, r-h column: "immunoprecipitated") merely demonstrates that truncated VSV G protein can be immunoprecipitated with a polyclonal anti-G antibody. Document (A16) shows (see page 146, legend to Figure 5) the reaction of bromelain-released HA with rabbit antisera against HA but it also shows that this truncated HA reacts with the antibody raised against the intact X-31 virus and with the antibody against the HA1 component only, which is a portion of HA. Should the skilled person conclude that eg. the HA1 component has the same primary, secondary, tertiary and quaternary structure as bromelain-released HA? The answer, in the Board's view, is clearly no. All these antibody-antigen reactions are too rough for proving that no alteration in the spatial conformation takes place upon truncation of a membrane-bound glycoprotein.

28. Rather, the Board is inclined to come to the opposite view. In document (X) (see paragraph on page 33 bridging the l-h and the r-h column), the authors discuss about the experimental finding that glycoprotein VP1 of foot-and-mouth disease virus (FMDV) produced by disruption of virus particles, is a very poor immunogen which fails to confer protection, while the virus particle does. They do not exclude, as a ground for this behaviour, the possibility that VP1 does not fold properly and thus does not present the correct immunodominant site to the immune system, once VP1 is deprived of the scaffolding provided by the other capsid proteins. The Board is of the opinion that removing VP1 from this scaffolding is a gentle operation when compared with truncation (which involves the removal of the truncated protein from the membrane **and** the removal of the transmembrane domain). Thus

document (X) would suggest to the skilled person that the mere fact of removing a glycoprotein from its natural environment might affect its three-dimensional conformation and that in the field of immunological response by a host, small changes in the three-dimensional conformation of an immunogen can have unpredictable effects on the immunogenic response. If this finding is valid for the mere removal of a protein from the particle, which operation does not alter the primary amino acid sequence of the protein, it is reasonable to assume that it should also be true for truncation of a viral membrane glycoprotein. This view is all the more reasonable if one bears in mind that the three-dimensional structure of a protein is that which gives the lowest free energy state. When a glycoprotein is embedded in a membrane, the free energy state and hence the conformation of the ectodomain is also influenced by its proximity to the membrane.

29. Also the appellants' second line of argument is not convincing. It is based on an alleged correlation between the ability of an antigen to elicit neutralizing antibodies and the ability of that antigen to protect an immunised host from *in vivo* virus challenge (see section VIII *supra*), which correlation is reinforced in cases where successful passive protection with these neutralizing antibodies has been shown, because in this case, cytotoxic T-cell response is not essential to protect the subject from attack.

30. As regards the appellants' proposition that "neutralizing antibodies equal immunoprotection", the Board finds useful to rely on the submissions by the appellants' experts themselves. Prof Enquist (see declaration dated 26 January 1995, paragraph 30) states that if glycoprotein D is reactive with a neutralizing antibody, it would be expected that glycoprotein gD

would elicit an immune response capable of **neutralizing** the relevant virus *in vivo* (emphasis added). The Board observes that Prof Enquist does not go so far as to speak about "protecting the host from an *in vivo* virus challenge". Prof Enquist's statement is in line with the one from another appellants' expert, Prof Roitt, who admits in the declaration dated 21 January 1995 (see paragraph 9) that with certain viruses, the presence of neutralizing antibodies might not be effective in preventing the spread of the viruses occurring by cell to cell transfer, circumstances in which the operation of the T-cell system (cellular immunity) would be required.

In any case, as regards Herpes simplex virus, before the earliest priority date of the patent in suit, the fact that neutralizing antibodies were a necessary but not sufficient condition for *in vivo* immunoprotection was confirmed by document (A4), (see page 192, l-h column, lines 7 to 11): "In humans, episodes of recurrent oral or genital Herpes virus infections occur regularly in the presence of circulating antibodies". Thus, the circulating antibodies, ie., the humoral response alone, were known to be insufficient for protecting the host from further virus infections. This was in line with the knowledge by the skilled person that a T-cell response was involved in immunoprotection elicited by Herpes simplex virus or by glycoprotein D thereof, although the mechanism by which this T-cell response mediated immunoprotection was still unknown to him or her (see paragraph 25 *supra*).

In view of this, the Board has to conclude that the skilled person would not have considered the appellants' proposition "neutralizing antibodies equal immunoprotection" as necessarily being true in the case of glycoprotein D of Herpes simplex virus. He or she

would have merely drawn the conclusion that glycoprotein D would have probably elicited an immune response capable of neutralizing the virus *in vivo*, a condition known to be necessary but not sufficient for protection.

31. As for the appellants' argument that successful passive protection with neutralizing antibodies further reinforces the proposition "neutralizing antibodies equal protection" because success in protecting a host with neutralizing antibodies means that a cytotoxic T-cell response is not essential to protect the subject from attack, it is noted that document (A3) (see page 1132, l-h column, lines 15 to 18 and page 1136, r-h column, lines 1 to 4) shows that the mechanism of passive immunisation goes beyond a mere reaction of the neutralizing antibody with the virus and involves in fact cellular elements. This document is concerned with investigating the mechanism(s) by which antibodies mediate protection in passive immunization. Another passage of document (A3)(see page 1132, l-h column, lines 1 to 9: "Mice immunosuppressed by irradiation, cyclophosphamide or antithymocyte serum were not protected by neutralizing antibodies") shows the importance of the cellular response.

32. However, in the Board's judgement, the skilled person had no valid reason for believing that these cellular elements evoked by injecting a host with a neutralizing monoclonal antibody were necessarily **the same** as the cellular response induced by immunising the host with glycoprotein D of Herpes simplex virus. The two situations are in no way comparable since, unlike a

single monoclonal antibody injected to the host, glycoprotein D induces a whole population of antibodies directed against any possible epitope, whose effect on immunoprotection was not known at the ealier priority date of the patent in suit.

33. Thus, as regards glycoproteins from Herpes simplex virus in general, while the skilled person looking for a vaccine against the virus would have considered as encouraging the facts that these glycoproteins or fragments thereof induce neutralizing antibodies and that passive immunisation with these antibodies is successful, he or she would not have deduced therefrom that vaccines comprising them would automatically have protected a host from an *in vivo* challenge with the virus. This, as seen above, was mainly because the mechanism by which the viral glycoproteins evoke a cellular response and contribute to immunoprotection *in vivo* is **very complex** (see document (A3), page 1136, 1-h column, third full paragraph and document (A11), page 351, 1-h column, last paragraph) and **not yet understood** (see point 25 *supra*).

34. Even in the unlikely assumption by the skilled person that the three-dimensional conformation of the gD-β-gal fusion protein of documents (Q) and (W) and of the KLH-gD-1 peptide conjugate of document (L) was similar to that of truncated glycoprotein gD (which assumption the Board denies in view of the conclusions of point 28 *supra*), both the facts that gD-β-gal fusion protein elicites neutralizing antibodies in animals and that the KLH-gD-1 peptide conjugate comprises a neutralizing epitope, would **not** have been taken by the skilled

person as an indication of *in vivo* immunoprotection by gD-β-gal fusion protein or by the KLH-gD-1 peptide conjugate, **let alone** by a recombinantly produced, truncated glycoprotein gD such as that according to claims 1 and 8 of the patent in suit.

35. In conclusion, the question raised under point 23 *supra* whether the skilled person, when applying the technique reported in document (A1) to the membrane glycoprotein D of Herpes simplex type 1 or type 2, would have reasonably expected that the resulting anchor-minus protein would have shown the property of immunoprotecting an immunised host against an *in vivo* challenge of Herpes simplex virus type 1 and/or type 2, is to be answered negatively. For these reasons, the subject-matter of claims 1 and 8 as well as that of dependent claims 2 to 7 and 9 of the fourth auxiliary request involve an inventive step.

36. Thus, the fourth auxiliary request is allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Opposition Division with the order to maintain the patent with the claims 1 to 9 according to the fourth auxiliary request and the description and drawings to be adapted thereto.

The Registrar: The Chairman:

A. Townend L. Galligani