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Datasheet for the decision of 4 March 2009

Case Number: T 0801/06 - 3.3.04

Application Number: 95927034.9

Publication Number: 0773785

IPC: A61K 35/76

Language of the proceedings: EN

Title of invention:
Treatment of cancer using HSV mutant

Patentee:
Crusade Laboratories Limited; The Wistar Institute of Anatomy and Biology

Opponent:
MediGene Aktiengesellschaft

Headword:
Cancer treatment with HSV mutant/CRUSADE

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2)

Keyword:
"Added matter (no); sufficiency of disclosure, novelty, inventive step (yes)"

Decisions cited:
T 067/97, T 0753/00, T 0609/02

Catchword:
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Case Number: T 0801/06 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 4 March 2009

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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 21 March 2006 concerning maintenance of European patent No. 0773785 in amended form.

Composition of the Board:

Chair: G. Alt
Members: R. Gramaglia
D. S. Rogers

Summary of Facts and Submissions

I. European patent EP-A-0 773 785 with the title "Treatment of cancer using HSV mutant" was granted with thirteen claims.

Claims 1, 9, 11 and 12 as granted read as follows:

1. Use of a mutant herpes simplex virus which has a non-functional γ34.5 gene in each long repeat region (R_L) in the manufacture of a medicament for use in treating a metastatic tumour which occurs in but does not originate from the central nervous system of a mammal.

9. Use according to any of claims 5 to 8 wherein the mutant virus is a mutant strain 17 virus.

11. Use of a mutant herpes simplex virus type 1 which has a non-functional γ34.5 gene in each long repeat region (R_L) owing to a deletion of 759bp in the γ34.5 gene, in the manufacture of a medicament for use in treating a melanoma cancer in a mammal.

12. Use according to claim 11 wherein the mutant virus is a mutant strain 17 virus.

The further claims 2 to 8 and 10 were dependent on claim 1; claim 13 was dependent on claim 11.

II. An opposition was filed under Article 100(a) to (c) EPC on the grounds of lack of novelty and inventive step, insufficiency of disclosure and added subject-matter.

The opposition division concluded that the feature in claim 9 "a mutant strain 17 virus" and the feature in claim 11 "treating a melanoma cancer" were not disclosed in the application as filed. Therefore claims 9 and 11 of the main request then on file, i.e. the claims as granted, contained added subject-matter. The opposition division maintained the patent on the basis of the claims of the first auxiliary request.

III. Both the patent proprietor (appellant I) and the opponent (appellant II) filed an appeal. Appellant I's statement of grounds of appeal was accompanied by a main request corresponding to the claims as granted and fourteen auxiliary requests.

IV. Each appellant filed a further submission in response to the other's statement of grounds of appeal.

V. Oral proceedings took place on 4 March 2009. Both parties were present.

Appellant I requested that the decision under appeal be set aside and that the patent be maintained upon the basis of, as a main request, claims 1 to 13 as granted or, alternatively, on the basis of one of the auxiliary requests 1 to 14 filed with the statement of the grounds of appeal.
Appellant II requested that the decision under appeal be set aside and that the European patent No. 0 773 785 be revoked.

VI. The following documents are mentioned in this decision:

D1: WO-A-96/00007

D2: Science, vol. 250, 1990, pages 1262-1266, Chou, J. et al.

D3: Neurosurgery, vol. 32, no. 4, 1993, pages 597-603, Markert, J.M. et al.

D4a: EP-A-0 514 603

D5: Molecular Genetics of Nervous System Tumors; Eds. Levine, A.Y. and Schideck, H.H.; 1993; "Viral vectors for experimental brain tumor therapy", pages 381-386, Martuza, R.L.

D11: WO-A-92/13943

D16: Human Gene Therapy, vol. 9, 1998, pages 2177-2185, Toda, M. et al.

D20: Cell, vol. 16, 1979, pages 481-494, Roizman, B.

D23: US-A-4,859,587; 22 August 1989

D24: WO-A-93/19591

VII. Appellant I's submissions in writing and during the oral proceedings, insofar as they are relevant to the present decision, can be summarized as follows:

Amendments

It was known that the herpes simplex virus (HSV) genome contained two copies of the γ34.5 gene and that the gene was involved in the neurovirulent phenotype of HSV. It was derivable from the whole content of the application as filed that the invention disclosed therein was based on the finding that rendering the γ34.5 gene non-functional provided HSV mutants effective in treating tumour cells and which did not cause encephalitis. Hence, in the context of the application as filed the reference to the modification of "a" γ34.5 gene or "the" γ34.5 gene had in fact to be understood as a reference to both copies of it. Therefore, the feature in claim 1 "a non-functional γ34.5 gene in each long repeat region" had a basis in the application as filed and therefore was an allowable amendment.

Although the HSV mutant strain 1716, a mutant strain derived from the HSV wild-type strain 17, was specifically named in the application as filed, it would be clear to the skilled person that this was by way of example in order to demonstrate the intended therapeutic effect. Therefore, the subject-matter of claim 9 did not extend beyond the content of the application as filed.

The description of the application as filed included the use of the γ34.5 mutant HSV for treating primary and

secondary, i.e. metastatic cancer. Moreover, Examples 1 to 5 concerned the treatment of melanoma cells. Therefore, the subject-matter of claim 11 relating to the use of a specific γ34.5 HSV mutant for treating melanoma cancer in general did not extend the content beyond that of the application as filed.

Sufficiency of disclosure

As evidenced by for example the disclosure in post-published document D16, the tumour model disclosed in Example 3 of the patent, i.e. mice bearing an intracranial tumour of melanoma cells, was an accepted animal model for the evaluation of agents for the treatment of metastatic brain cancer. Appellant II had not submitted any verifiable facts supporting its submission that this model was not suitable to reflect the claimed therapeutic application.

Novelty

When considering the teaching in the international application D1 as a whole, the use of a HSV γ34.5 mutant for the treatment of non-nervous-system-type tumours having metastasised to the central nervous system was not derivable from it.

It was clear to the skilled person that a "metastatic tumour" was one occurring in but not originating from a particular tissue in the **same** animal. Thus, the tumours disclosed in document D3 artificially created by implantation of primary central nervous system (CNS) derived tumour cells from the brain of a human being to

the brain of a mouse did not fall under the tumour definition in claim 1.

Hence, neither the international application D1 nor document D3 were relevant to the novelty of the subject-matter of any of the claims.

Inventive step

Document D3 disclosed, inter alia, animal studies investigating the effect of a γ34.5 deletion mutant HSV, R3616, on the treatment of glioma, i.e. primary brain tumours.

The problem to be solved in view of document D3 was whether the γ34.5 mutant HSV approach could be successfully applied to the treatment of tumours originating from tissue other than neuronal tissue but occurring in the CNS. With regard to claim 11 the problem was whether the γ34.5 mutant HSV approach could be applied in the treatment of melanomas.

Document D3 investigated CNS-cell-derived tumours in the brain. Therefore, the subject-matter of none of the claims could be considered as obvious in the light of document D3 alone.

Also the general disclosure in documents D4a and D24 that HSV mutants were suitable for treatment of all types of tumours did not render the claimed subject-matter obvious. Firstly, HSV was considered to be a neurotrophic virus in its natural host. Secondly, although it was known from document D2 that γ34.5 HSV mutants generated a lytic infection in cells of non-

neuronal tissue in cell culture, the skilled person had no reasonable expectation that this would also occur if these cells were part of host tissue. Finally, none of documents D4a or D24 contained any data supporting the suggested oncolytic effect of the HSV mutants in cells other than cells derived from neuronal tissue.

VIII. Appellant II's submissions, in writing and during the oral proceedings, insofar as they are relevant to the present decision, can be summarized as follows:

Amendments

It was known that HSV wild-type strains contained two copies of the γ34.5 gene. For that reason, it was ambiguous whether the application as filed when referring to "a" or "the" γ34.5 gene, in fact referred to a deletion in only one or in both copies of it. This was the more so, since HSV mutants lacking only one copy of the γ34.5 gene were known, for example, from document D23. Moreover, reference 15 of the application as filed was cited in the application in the context of a disclosure of γ34.5 "null mutants". Reference 15 disclosed the HSV-1 mutant "RE6". It was known at the priority date of the patent that the introduction into the RE6 mutant genome of a DNA sequence containing a copy of the γ34.5 gene reconstituted the neurovirulent phenotype of RE6. However, this did not necessarily mean that the HSV RE6 genome had a deletion in both copies of the γ34.5 gene. The original neurovirulent phenotype would also be reconstituted if RE6 had only one mutated γ34.5 copy. Therefore, also the term "null-mutant" in the application as filed could not be

regarded as a clear and unambiguous description of a γ34.5 double mutant. Finally, documents D1 to D3 when referring to the γ34.5 gene always used the plural. For all these reasons the reference in claim 1 to a non-functional γ34.5 gene in each long repeat region was an amendment contravening the requirements of Article 123(2) EPC.

The application as filed only disclosed one specific strain 17 virus mutant which was also used in the framework of the examples, i.e. the mutant strain "1716". Under these circumstances, the generalisation of this specific example was not allowable. This view was also supported by the case law, for example decision T 753/00. The subject-matter of claims 9 and 12 relating to the use of a mutant strain 17 virus was therefore not derivable from the application as filed.

Example 1 disclosed that the HSV mutant 1716 lysed cultured melanoma cells. This example could however not support claims relating to in vivo melanoma tumour treatment. Examples 2 to 5 concerned the treatment of secondary melanoma tumours in the brain. Hence the subject-matter of claim 11 which related to the treatment of melanoma tumours in general, i.e. also included the treatment of primary melanoma, had no basis in the application as filed.

Sufficiency of disclosure

The relevant assays presented in the patent were carried out with either cultured melanoma cells (Example 1) or with mice having tumours of human melanoma cells artificially implanted in the brain

(Examples 3 to 5). Thus, since the patent contained no data of the application of a γ34.5 mutant virus to a "real" metastatic tumour, i.e. one which was generated by a true metastasising process in the same organism, the disclosure in the patent did not fulfil the requirements of Article 83 EPC.

Novelty

The international application D1 disclosed on page 6 that CNS- and non-CNS-type tumour cells could be killed by an altered HSV which according to page 5, lines 29 to 31 had inter alia a non-functional γ34.5 gene product. On page 9 it was disclosed that the invention disclosed in the international application also related to methods for testing the ability of the altered virus to kill tumour cells **in the brain**. If these cells were non-CNS cells situated in the brain as suggested by the disclosures on page 6, such a tumour was to be regarded as a "metastatic" tumour. Therefore, the disclosure in document D1 anticipated the subject-matter of claim 1.

In the context of the patent the term "metastatic tumour" had to be broadly interpreted as being a tumour consisting of any cell type which is in at least one aspect foreign to the CNS of a particular organism. Therefore, the use of a mutated γ34.5 HSV for the treatment of mice carrying glioma consisting of **human** cells as disclosed in document D3 destroyed the novelty of the subject-matter of claim 1.

Inventive step

Document D3, the closest prior art document, disclosed two different animal tumour models, i.e. mice bearing either an intracranial or subcutaneous human glioma, i.e. a tumour consisting of human cells derived from neuronal tissue. The first model reflected the treatment of tumours in the brain consisting of neuronal cells, i.e. of primary CNS tumours whereas the second model reflected the treatment of metastatic glioma, i.e. glioma tumours which were not situated in the brain. In both cases the problem to be solved could be formulated as the treatment of metastatic tumours in the brain.

The patent did not reveal data obtained by treating a "real" metastatic tumour and therefore did not demonstrate that the claimed subject-matter actually solved the problem. Therefore, the claimed subject-matter lacked an inventive step.

Furthermore, the subject-matter of all claims lacked an inventive step in view of the disclosure in document D3 alone or in combination with the disclosure of either of documents D4a or D24.

The animal studies in document D3 essentially demonstrated that tumour cells surrounded by a cell type different therefrom, i.e. foreign tumour tissue could be treated with the HSV mutant R3616 which had deletions in both copies of the γ34.5 gene.

Document D4a related to the use of HSV mutants for cancer treatment and in its broadest aspect did not

disclose a restriction as to the type of tumour to be treated.

Document D24 disclosed on page 10, lines 29 to 32 that an "HSV-1 virus with a specific mutation in the γ34.5 gene provides a method of therapeutic treatment of tumorogenic diseases both in the CNS and in all other parts of the body".

Thus it was suggested by either of document D4a or D24 to use the HSV mutant approach for the treatment of any type of tumour. Consequently, the claimed subject-matter was obvious.

Reasons for the Decision

Amendments

1. Appellant II argues that claims 1, 9, 11 and 12 contained subject-matter extending beyond the content of the application as filed.

Claim 1: a non-functional γ34.5 gene in each long repeat region

2. Appellant II submits that the feature in claim 1 that the mutant herpes simplex virus (HSV) has a non-functional γ34.5 gene in **each** long repeat region is neither explicitly disclosed in the application as filed nor is it implicitly disclosed so as to be clearly and unambiguously derivable from it.

3. As to the term "long repeat region", it is known that the HSV genome consists of two covalently linked fragments of different length, each containing largely unique sequences which are termed "UL" and "US". Each of the "U" fragments is flanked by a pair of nucleic acid segments containing largely the same sequence information, but in inverted orientation. Since these segments are located at the termini of the U fragments, they are denoted "inverted terminal repeats". The segments flanking the "UL" are denoted "RL" (or "long repeat region") and those flanking the US are called "RS" (or "short repeat region"; see for example the application as filed, page 1). Thus, due to this genomic arrangement, genes situated within the repeat regions, such as for example the γ34.5 gene, are present in two identical copies in wild-type HSV.

4. In the patent in suit the mutant HSV is described as comprising **a** modification in **the** γ34.5 gene in the long repeat region or by a similar, singular-type wording (for example claim 1 as filed). In other words, a mutant HSV with a modification in only one of the γ34.5 genes is disclosed explicitly.

5. However, as established by the case law, when determining the disclosure content of the application as filed for the purposes of Article 123(2) EPC, the implicit disclosure also has to be taken into account. The implicit disclosure is the information conveyed by a document to the skilled person when reading the explicit information in the light of the common general knowledge. (Case Law of the Boards of Appeal of the EPO, 5th edition, III.A.1.1).

6. When reading the present application one thing that the skilled person would notice is that with regard to the γ34.5 gene and modifications therein the singular is consistently used and in particular also, when reference is made to the well-known γ34.5 double mutant strains R3616 and 1716, or when referring to the HSV wild-type genome which, as is well-known (see point 3 above), has two copies of the γ34.5 gene: "The terminal 1 kb of the long repeat region (R_L) of the HSV-1 and HSV-2 genomes contain **a** gene (11-13), that confers neurovirulence." (page 3, lines 11 to 13; emphasis added).

7. Moreover, the skilled person would derive from the application as filed that the invention disclosed therein relates to the therapeutic use of a HSV having a modification in the γ34.5 gene such that the gene is "non-functional" (for example claim 1 as filed).

8. On page 5 of the application as filed the meaning of "non-functional" is explained:

"For the purposes of the present invention "non-functional" means that the gene has been modified by deletion, insertion or substitution (or other change in the DNA sequence such as by rearrangement) such that it does not express the normal product or a functionally equivalent product. The effect of the non-functionality of the gene is that the neurovirulence of the virus to the patient is substantially removed."

Moreover, it is stated on page 5 that "the invention is based on the finding that rendering the γ34.5 gene non-functional provides an HSV mutant which is particularly

effective in destroying dividing tumour cells, whilst at the same time the HSV mutant does not replicate within normal non-cancerous cells. It therefore has the potential to provide a safe anti-cancer treatment."

9. The skilled person knows from the prior art that one of the severe complications of an HSV infection is encephalitis (for example document D2, page 1262, left, column). Moreover he/she knows that mice infected with the HSV mutant R3616 which is known to have deletions in both copies of γ34.5 gene (see document D3, page 598, first column, second full paragraph) have been found not to develop encephalitis (see document D3, Abstract, lines 12 to 13) and that therefore the γ34.5 gene or its protein product is considered responsible for the neurovirulent phenotype of HSV.

10. In the light of this knowledge, the skilled person would therefore derive from the disclosure of the invention in the application as filed as a whole and in particular from the passages cited in point 8 above that, in order to be safe for the intended therapeutic application, the function of the γ34.5 gene has to be completely suppressed. Given that there are two copies of the gene the skilled person would understand that this effect is only achieved if both copies of the gene are made non-functional.

11. In the board's view, due to this understanding of the invention, the skilled person also had no doubt that the term "null mutant" appearing on page 3 of the application as filed has to be given its ordinary meaning, namely that a "null mutant" is an organism which phenotypically completely lacks a particular

function. He/she would therefore not have considered, as argued by appellant II, that the term could also refer to a virus with a modification in only one copy of the γ34.5 gene. For the same reason, the skilled person would not be influenced by the disclosure, for example in document D23, of avirulent HSV variants lacking only one copy of the γ34.5 gene and also not by the fact that a more precise language for the description of γ34.5 double mutants is used in documents D1 to D3.

12. The board notes in passing that in document D2 the HSV γ34.5 double mutant R3616 is described in Table 1 as having a "1000bp deletion in **the** γ34.5" (emphasis added) which demonstrates, in the board's view, that it is not unusual to use the "imprecise" singular form when actually intending to refer to both copies of the γ34.5 gene.

13. In summary, when taking account of the disclosure in the application as filed as a whole the skilled person would have implicitly derived therefrom that the γ34.5 gene is non-functional due to a modification in **both** copies of the γ34.5 gene. Therefore, the board concludes that the feature in claim 1 "a non-functional γ34.5 gene in each long repeat region (R_L)" has a basis in the application as filed. Therefore, the subject-matter of claim 1 does not extend beyond the content of that application.

Claims 9 and 12: "a mutant strain 17 virus"

14. As to the meaning of the term "strain 17 virus", the skilled person knows that the HSV genomic DNA is highly variable. It is for example disclosed in review document D20, page 483 in the middle of the second column that "no two epidemiologically unrelated isolates of HSV-1 were identical" and that it is predicted that there are "at least 2^{10} differentiable virus strains in the human population". Thus, there are many different wild-type HSV strains. Strain 17 is one of the HSV-1 strains that has been found in nature. It is one of the widely used HSV laboratory strains.

15. Appellant II argues that the disclosure in the application as filed is limited to the use of the only disclosed strain 17 mutant, i.e. 1716 and that there was no basis for generalisation of this teaching.

16. In the board's view, the skilled person would understand from the application as filed as a whole that the essence of the invention is the non-functionality of the γ34.5 gene (see above points 7 to 10). In particular, due to, for example, claim 1 which is not restricted to the use of a specific HSV strain, but relates to the use of any mutant HSV with a modification in the γ34.5 gene the skilled person would perceive that the invention is not based on the combination of a specific HSV virus strain and a non-functional γ34.5 gene. Consequently, in the board's view, the skilled person would derive from the application that the strain 17 mutant "1716" which has a 759 bp deletion at a particular position in the γ34.5 gene (page 4 of the patent and document D11, pages 20 and 21)

is only an example. Thus, the skilled person would consider that the use of other strain 17 derivatives with modifications in the γ34.5 gene differing from the one in strain 1716 but which render the γ34.5 gene non-functional is comprised by the disclosure content of the application as filed.

17. This conclusion is in line with established case law that features from specific examples may be extracted and put in a more general context provided that such a generalisation is evident to the skilled person (Case Law of the Boards of Appeal. 5th Edition, III.A.1, page 240, last three paragraphs). This conclusion can also be drawn from decisions T 753/00 of 2 June 2003 and T 1067/97 of 4 October 2000. In decision T 753/00, referred to by appellant II, the board denied the isolation of a feature which was disclosed in the context of an example because its general applicability could not be inferred from the application as filed (point 27 of the reasons). In decision T 1067/97, referred to in decision T 753/00, the isolation of a feature from the specific context was not permitted because the feature was part of a particularly preferred embodiment of the claimed invention, which embodiment was characterised by a set of features which the skilled person would clearly consider as being interrelated (points 2.1.2 and 2.1.3 of the reasons).

18. Therefore, the board concludes that the feature in claim 9 "a mutant strain 17 virus" has a basis in the application as filed. Therefore, the subject-matter of claims 9 and claim 12 does not extend beyond the content of that application.

Claim 11: "for treating a melanoma cancer"

19. Appellant II argues that the application as filed discloses the treatment of melanoma metastases in the brain, but not the treatment of primary melanoma tumours. (As to the terms "primary melanoma tumour and "metastatic melanoma" see also below point 48).

20. However, there are several passages in the application as filed referring to the use of the mutant herpes viruses according to the invention for the treatment of cancer in general. For example, it is disclosed on page 1, lines 1 to 5 that "the present invention relates to the use of a herpes simplex virus (HSV) mutant for the treatment of cancer tumours, [...] whether the tumours are metastatic tumours or primary tumours". On page 4, lines 21 to 5 it is stated: "The present invention [...] provides the use as an anticancer agent of a mutant herpes simplex virus [...]." Similarly claim 1 as filed relates to the treatment of any type of tumour.

21. On page 4, line 11, before carrying on to the subject of cerebral metastases of melanoma, it is stated that "melanoma is a prevalent malignancy", which statement, in the board's view, would also indicate to the skilled person that melanoma treatment outside the CNS is contemplated by the application as filed.

22. The examples of the patent in suit further support the board's view.

22.1 First, Example 1 demonstrates that the HSV mutant 1716 infects and lyses melanoma cells in cell culture, a

result that would be considered by the skilled person as reflecting the treatment of both primary or metastatic melanoma.

22.2 Second, Example 3 discloses the infection of mice bearing intracranial tumours of human melanoma cells with the HSV mutant 1716.

Normally, the skilled person would consider these animals as experimental models for metastatic tumours (see point 29.2 below).

However, in the present case, the skilled person derives from the application as filed as a whole that the invention disclosed therein relies on the property of γ34.5 gene-mutated HSV to infect and lyse a given tumour cell type. Moreover, the skilled person is aware from the prior art that until the priority date of the patent no use, or attempt to use, mutated HSV for the infection of melanoma cells had been made (see point 70 below). Given these circumstances, in the board's view, the skilled person would not have considered the teaching of the Example 3 to be restricted to metastatic tumours, but would also have derived from it the more general teaching that melanoma cells are permissive for the replication of HSV with a non-functional γ34.5 gene.

23. Thus, the board concludes that the feature "for treating a melanoma cancer" has a basis in the application as filed and that therefore the subject-matter of claim 11 does not extend beyond the content of that application.

24. The requirements of Article 123(2) EPC are therefore fulfilled.

Sufficiency of disclosure

25. According to Article 83 EPC a European patent "shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The present invention is directed to a second medical use. According to the case law in order for the requirements of Article 83 EPC to be fulfilled with regard to an invention relating to a second medical use, it is required that the skilled person knows, either from the disclosure in the patent and/or the common general knowledge, how to prepare the used compound and moreover that there is evidence, either in the patent and/or from the common general knowledge, for the claimed therapeutic effect (for example T 609/02 of 27 October 2004, point 9 of the reasons).

26. In the present case it is not contested that the skilled person knows how to produce any of the mutant viruses referred to in the claims. Rather, appellant II argues that experimental support for the therapeutic effect to be achieved according to claim 1, i.e. the treatment of a "metastatic tumour which occurs but does not originate from the central nervous system of a mammal", is lacking in the patent in suit because the patent does not contain data obtained from assays with a "real" metastatic tumour, i.e. one which has been formed after a true metastasing process, i.e. after migration of tumour cells in the same body.

27. Example 1 discloses the infection of cultured melanoma cells with HSV strain 1716, i.e. a mutant HSV having a deletion of 759 base pairs in each copy of the γ34.5 gene. Moreover, in Example 3 the intracranial infection with HSV 1716 of nude mice bearing melanoma cell tumours in the brain which were established by injecting cells of a melanoma cell line into the mouse brain is disclosed. Thus, the therapeutic effect is assessed either in vitro in cultured cells or in vivo with an animal model.

28. It has been established by the case law relating to sufficiency of disclosure with regard to claims to a second medical use and to which the present board adheres, that a claimed therapeutic effect may be proven by any kind of data as long as they clearly and unambiguously reflect the therapeutic effect (for example T 609/02 of 27 October 2004, point 9 of the reasons and decisions cited therein).

28.1 Thus, the fact per se that the experiments in the patent were not carried out with a "real" metastasis is not sufficient to deny sufficiency of disclosure.

29. As to the clear and unambiguous reflection of the intended therapeutic effect, the board concludes from the prior art that in vitro cell culture assays and in particular animal tests with nude mice bearing artificially created tumours of, for example, human cells are a well-recognized system for testing the oncolytic capabilities of mutated herpes virus.

29.1 Document D5, a review article about viral vectors for experimental brain tumour therapy, and document D3

disclose studies with HSV mutated at the γ34.5 locus. The virus' potential usefulness for the therapy of primary brain tumours is evaluated by infection of mice bearing intracranial tumours of human glioma cells. Both documents also disclose cell culture assays in the same context (document D5, page 385, second column, first full paragraph and document D3, "Results").

29.2 Moreover, in the post-published document D16 the efficacy of a γ34.5 mutant for treatment of metastases of breast cancer is evaluated in cultured breast cancer cells and in a mice bearing subcutaneous and intracranial breast cell tumours.

30. In these circumstances and given that appellant II's argument was not supported by any evidence, i.e. verifiable facts in the sense of decision T 19/90 (OJ EPO 1990, 476, point 3.3) that, for example, the infectious and replicative properties of the mutant HSV virus are dependent on the way in which the metastasis is generated, the board has no reason to doubt that the assays disclosed in the patent are suited to clearly and unambiguously reflect the intended therapeutic application, i.e. the treatment of metastatic brain tumours.

31. The results of the assay disclosed in Example 1 show that the HSV mutant virus strain 1716 lyses cultured melanoma cells. The result of the animal tests according to Example 3 is that melanoma tumour bearing mice treated with the HSV mutant virus strain 1716 have a longer life time than non-treated animals. Moreover, examination of the brain of the survivors did not reveal any residual tumour. Moreover it was found that

replication was restricted to tumour cells (Examples 4 and 5). In the board's view, these results demonstrate the very effect on which the use of claim 1 relies.

32. No further arguments with regard to insufficiency of disclosure were submitted, in particular with regard to the subject-matter of claim 11 relating to the treatment of melanoma cancer. The board also has no further objections of its own, for the reasons given in points 22.1, 22.2 and 31 above.

33. The requirements of Article 83 EPC are thus fulfilled.

Novelty

International application D1

34. The international application PCT/US95/07858 (hereinafter "the international application D1") designates inter alia the European Patent Office. The application has entered the European phase. With the exception of the Contracting State Liechtenstein (LI) the international application D1 designates the same states as the patent in suit. The priority date claimed by this international application is 23 June 1994. The priority date of the patent is 29 July 1994. Appellant I did not contest the validity of the priority claimed by document D1. The board has no objections either. Therefore, the international application D1 belongs to the state of the art pursuant to Article 54(3) EPC in connection with Articles 150(3) and 158(1) EPC 1973.

35. The international application D1 relates to the use of an altered HSV that is capable of killing tumour cells

(page 1, first sentence). According to page 5, lines 29 to 31 such a virus has inter alia a non-functional γ34.5 gene product. After having stated that the tumour cells to be killed can be of a nervous-system type, the international application D1 discloses on page 6, lines 9 to 15 that "other kinds of tumor cells which can be killed, pursuant to the present invention, include those selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, breast cancer cells, lung cancer cells, colon cancer cells, lymphoma cells, hepatoma cells and mesothelioma and epidermoid carcinoma cells." . Moreover it is disclosed on page 9, line 15 that the invention provides methods for "testing viruses for the ability to effectively kill brain tumour cells".

36. Appellant II submits that, in the light of the statements cited above, the skilled person would have considered that the international application discloses viruses for killing tumours of the type mentioned on page 6 in the brain, and which, since the tumours referred to on page 6 are non-central nervous system type tumours, are consequently to be regarded as "metastatic" brain tumours. Therefore, the international application D1 anticipated the subject-matter of claim 1.

37. The board does not agree with appellant II's interpretation of the disclosure of the international application D1.

38. Firstly, the term "brain tumour" without any qualification of the cell type or the location is normally used to denote tumours of neuronal cells

situated in the CNS, i.e. primary brain tumours. For example, in document D3 relating to the investigation of a therapy for primary brain tumours (see points 45 to 51 below) the term is used when referring to these tumours, see for example the first sentence of the abstract reciting "malignant brain tumors" or the last sentence of document D3 reciting "brain tumors". The same expression for describing primary brain tumours is used in document D5, for in example in the title, reading "Viral vectors for experimental brain tumor therapy".

39. Moreover, in the board's view, the skilled person would not have considered that the disclosure in the international application D1 when taken as a whole, relates in any way to the treatment of metastatic brain tumours.

40. This is so, in the board's view, firstly, because the description of the prior art with regard to the tumours to be treated by the altered HSV relates entirely to primary tumours of the central nervous system (see page 1, second and third paragraph).

41. Secondly, under the heading "Summary of invention" it is set out in the paragraph bridging pages 4 and 5 that "the object of the present invention is to provide for [...] the treatment of malignant brain tumors in humans". After explaining in the first full paragraph on page 5 that a further object of the invention is that the vector should be safe, it is then stated in the second paragraph that "[s]till another object of the present invention is to provide a mutant HSV-1

vector that can selectively replicate in and kill a tumor cell of non-nervous tissue origin".

41.1 Thus, this passage highlights the difference between killing "a tumor cell of non-nervous tissue origin" on the one hand and killing "malignant brain tumors", i.e. tumour cells of nervous tissue origin, on the other. A corresponding differentiation is found in the passage starting at the bottom of page 5 and which ends on page 6 with the statement relied on by appellant II.

In the board's view, due to the skilled person's understanding of the term "malignant brain tumors" as meaning "primary tumors of nervous tissue" (see point 38 above) and even more, due to explicit enumeration of tumours to be treated in the passage on pages 5 and 6, the skilled person would have considered that the essence of the difference between the first and second aspect of the invention lies in the type of tissue, i.e. neuronal versus non-neuronal tissue and not in the location, i.e. primary versus metastatic tumours.

42. Finally, in the examples of the international application D1 the effect of the altered HSV is assessed with two animal models, i.e. nude mice having implanted human glioma cells in the subrenal capsule and nude mice carrying human glioma intracerebrally. Both would be considered by the skilled person as imitating the situation of a primary neuronal cell tumour (see points 45 to 51 below).

43. Thus, the board considers that when taking into account the disclosure in the international application D1 as a

whole, the skilled person would not have derived from it the disclosure of the use of a mutant HSV for the treatment of a metastatic tumour which occurs in but does not originate from the central nervous system of a mammal.

44. Consequently, the subject-matter of claim 1 and dependent claims 2 to 10 is novel over the disclosure in the international application D1.

Document D3

45. Document D3 reports an animal study aiming at determining the effectiveness of HSV mutants for the treatment of glioma. Gliomas are primary tumours in the brain (first sentence of document D3). Two different types of test animals which in the document are considered as experimental models for glioma therapy (see the title of the document) are disclosed, i.e. nude mice carrying either subcutaneous or intracranial glioma consisting of human cells. The tumours in the mice were generated by inoculating human glioma cells from a cultured cell line either subcutaneously or into the right frontal lobe of the mice. Mice were treated with, inter alia, the virus R3616, a HSV mutant having a 1 kb deletion in both copies of the γ34.5 gene (see page 598, first column, second full paragraph).

46. Appellant II argues that in the light of the German translation of claim 1 saying that the virus according of the invention is for the treatment of a metastatic tumour "der im Zentralnervensystem auftritt, aber einen **anderen Ursprung** hat" (emphasis added), in the light of paragraph [0022] of the patent stating that the HSV

treatment was useful "against metastatic tumours where cancer cells **originating elsewhere** have lodged in the brain or nervous system" (emphasis added) and in the light of the examples disclosing mice with tumours in the brain consisting of cells that do not stem from mice, the term "metastatic tumour" has to be interpreted as referring to a tumour consisting of cells which are in the broadest sense "foreign" with regard to the surrounding tissue. Therefore, the tumours of the experimental mice according to document D3 carrying intracranial glioma of **human** cells have to be considered as falling under the definition of "metastatic tumour" according to claim 1 the subject-matter of which was therefore not novel in view of the disclosure in document D3.

47. However, firstly, it follows from Article 14(9) EPC that terms in a patent are interpreted on the basis of the patent in the language of the proceedings and not on the basis of the translated version. The board notes however, that it would not have come to a different conclusion in the present case (see below) if an interpretation on the basis of translated claim 1 was permissible.

48. Secondly, the term "metastatic tumour" has a well-known meaning, i.e. it refers to a tumour, consisting of cells that have detached from a primary tumour situated in one part of the body of an organism and that have migrated to a different part of the body in the same organism to form a tumour, i.e. a metastasis.

49. The skilled person would have no doubt that the patent in suit as far as it relates to the treatment of

metastasis, aims at treating patients having metastases in the central nervous system, i.e. metastases in the normal medical sense. Therefore, in the board's view, it would be clear to the skilled person that when the patent refers to "originating elsewhere", it does not mean anything else than "elsewhere in the same body".

50. Thus, the board is convinced that the expression "metastatic tumour which occurs in but does not originate from the central nervous system" in claim 1 is not to be interpreted such as to read onto the "artificial" human, nervous-system-cell derived tumours in the brain of mice according to document D3.

51. Consequently, the disclosure in document D3 does not anticipate the subject-matter of claim 1 and dependent claims 2 to 10.

52. The subject-matter of the further independent claim, claim 11, relates to the "use of a mutant herpes simplex virus type 1 which has a non-functional γ34.5 gene in each long repeat region (R_L) owing to a deletion of 759bp in the γ34.5 gene, in the manufacture of a medicament for use in treating a melanoma cancer in a mammal".

53. Appellant II did not raise any objection of lack of novelty with respect to this claim. The board has no objections itself. In particular, with regard to document D1 it is noted that it does not disclose the

54. specific virus referred to in claim 1. Thus, the subject-matter of claim 11 and dependent claims 12 and 13 is considered to be novel.

55. The requirements of Article 54 EPC are thus fulfilled.

Inventive step

Closest prior art - problem - solution

56. Document D3, the only document referred to as closest prior art document by the parties, discloses an experimental animal study aiming at evaluating the effectiveness of, inter alia, HSV mutants having a non-functional γ34.5 gene due to a deletion in both of its copies (mutant R3616, see page 598, in the middle of first column) for the treatment of glioma, i.e. primary tumours of the brain (see also point 45 above). Although two different murine tumour models are disclosed - subcutaneous and intracranial U87 human glioma cell xenografts - both actually serve the same purpose, i.e. to investigate the influence of the γ34.5 virus mutant on the development of tumours derived from neuronal tissue (see for example page 598, first column, last paragraph). Therefore, in the board's view, the problem to be solved vis-à-vis the disclosure in document D3 may be formulated as the provision of an alternative use for an HSV mutant having a non-functional γ34.5 gene due to a deletion in both of its copies.

57. According to claim 1 the solution to this problem is the use of such a mutant for the manufacture of a medicament for the treatment of a metastatic tumour

which occurs in but does not originate from the central nervous system of a mammal. According to claim 11 the solution to this problem is the use of an alternative HSV mutant for the treatment of melanoma cancer.

Evidence that the problem is solved by the claimed solution

58. For the reasons given in points 25 to 32 above the board is satisfied that the patent demonstrates that the claimed subject-matter solves the problem formulated above.

Obviousness

Claim 1

59. Appellant II argues that the subject-matter of claim 1 is obvious in view of the closest prior art document D3 alone or in view of a combination of document D3 with either of documents D4a or D24.

Document D3

60. According to appellant II the situation disclosed in the animal model according to document D3 that a γ34.5 mutant HSV induces regression of tumours composed of cells stemming from a mammal different from the tumour bearing one is not much different from the situation of a metastatic tumour in the brain because in both instances the tumour cells are "foreign" compared to the surrounding cells.

61. However, firstly, the skilled person would understand that document D3 deals with treatment of primary brain

tumours (see points 45 and 55 above) and would consider the glioma-bearing mice as disclosed in document D3 as experimental models for the therapy of tumours of neuronal cells. Thus, the skilled person would not derive from the disclosure in document D3 the suggestion that a mutant HSV which has a non-functional γ34.5 gene in each long repeat region can be used for the destruction of tumours consisting of non-neuronal cells located in the brain.

Documents D4a and D24

62. Document D4a, a European patent application, reveals in particular that an HSV mutant lacking thymidine kinase gene expression is capable of selectively replicating in glioma cells, but not in normal brain cells. By way of a general disclosure it is stated in column 4, lines 19 to 24 that "according to a first aspect of the present invention there is provided the use of an altered virus which is capable of replication in **neoplastic** cells, but not in normal cells in the preparation of an anticancer agent or an agent for selectively killing neoplastic cells." (emphasis added). According to column 5, neoplastic cells "include cells of tumours, neoplasms, carcinomas, sarcomas, leukemias, lymphomas and the like".

63. Document D24, an international patent application, deals with the influence of the HSV γ34.5 gene on programmed cell death ("apoptosis"). It is reported that the γ34.5 gene is responsible for prolongation of cell life. In turn, it is therefore concluded that an HSV mutant lacking the gene could be useful to induce cell death in tumour cells. It is stated on page 10,

lines 29 to 32 that "[i]n addition, use of the HSV-1 virus with a specific mutation in the γ34.5 gene provides a method of therapeutic treatment of tumorogenic diseases both in the CNS and **in all other parts of the body**." (emphasis added).

64. Appellant II argues that the skilled person would be motivated to use the HSV γ34.5 deletion mutant disclosed in document D3 for the treatment of metastatic tumours which occur in but do not originate from the central nervous system, by either the disclosure in document D4a (exemplified by the statement above) that is not restricted to any specific tumour cell type or by the statement in document D24 cited above referring to the use of HSV mutant for tumour treatment in all other parts of the body.

65. In order to assess the motivation of the skilled person in view of the disclosure in either of documents D4a or D24, the disclosure has to be regarded in entirety and has to be interpreted from the point of view of the skilled person taking into account his/her knowledge of the prior art at the relevant priority date.

66. On the basis of the common general knowledge, the skilled person would consider HSV as a neurotrophic virus, the reason being that the virus generates a latent infection in neurons and that it causes encephalitis (D11, page 1, lines 11 to 18; D24, page 42, lines 28 to 33).

67. Moreover, at the priority date the skilled person would be aware not only of the teaching from documents D4a and D24 but also of, for example, that in documents D3

and D5, which also relate to studies investigating the effectiveness of HSV mutants for cancer treatment.

68. As already observed above document D3 investigates glioma cancer and discloses only the infection of glioma cells. Also document D5, a review article relating to viral vectors for experimental brain tumour therapy, reports in the context of HSV mutants only on the studies relating to tumours of the nervous system (see pages 384 and 385). In the last paragraph of the second column on page 385 it is for example stated: "Nonetheless, these data, taken collectively provide evidence that this strategy can be used to kill intracranial tumour cells of a variety of nervous system tumors with relative sparing of the surrounding brain cells".

69. As to the disclosure in document D4a when considered in its entirety, the skilled person would derive from it that it is focused on nervous system tumours. It is for example stated in column 5, lines 21 to 49, immediately after the general reference to "neoplastic cells" cited above that nervous system tumours are of particular interest. In lines 28 to 49 of column 5 the need for the development of a glioma therapy is set out. The examples section starts with the sentence "glioblastomas are the most common form of malignant brain tumours in man, and are almost always universally fatal. In the worked examples infectivity of Vero cells with a specific HSV thymidine kinase mutant has been studied in addition to two different glioma cell lines. However, these cells were included in the assay as a control because HSV was known to replicate in Vero cells (see column 12, lines 10 to 12: "Viruses were

grown and titered on Vero cells as previously described".) Finally, the animal studies were carried out with rats bearing tumours of U87 cells, i.e. cells from a human glioma cell line.

70. As for the disclosure of document D24, the skilled person would notice, first, that tumour therapy by removal of γ34.5 function from HSV forms only a minor part of the disclosure. In fact, most of the document deals with the opposite use of γ34.5, namely the prolongation of cell life. In the latter context all the suggested therapeutic applications concern cells of the nervous system. It is for example stated on page 9, lines 13 to 27: "An appreciation of this extra dimension of protection can be utilized in novel and innovative means for control and treatment of central nervous system (CNS) disorders. Specifically, treatment of CNS degenerative diseases, including Alzheimer's disease, Parkinson's disease, Lou Gerig's [sic] disease, and others the etiology of which may be traceable to a form of apoptosis, and the treatment of which is currently very poor, could be improved significantly through the use of either the γ34.5 gene in gene therapy or the protein expressed by γ34.5 as a therapeutic agent."

Moreover, the only worked example of the six examples disclosed in document D24 is designed to reveal whether or not HSV-1 recombinant viruses lacking the γ34.5 gene induce the shut off or protein synthesis in cells of a neuronal cell line, i.e. neuroblastoma cells.

71. Thus, when considering the prior art at the priority date of the patent as represented in these proceedings

by documents D3, D4a, D5 and D24 the skilled person would have been aware that the existing line of research relating to use of HSV mutants for treatment of cancer was exclusively concerned with CNS-cell derived tumours. Moreover, the skilled person would notice that none of documents D4a and D24 gives any experimental support for the use of HSV mutants for treating tumours in general.

72. As further evidence for the non-allowability of the claims of the main request appellant II referred to document D2. It discloses on page 1264, last column, last paragraph that "plaque morphology and size of all the recombinants were similar to those of the wild-type parent, HSV-1(F), when plated on Vero, 143TK$^-$ and rabbit skin cells.". Appellant II argues that since (i) Vero cells are epithelial kidney cells, 143TK$^-$ are human osteosarcoma cells and rabbit skin cells are epithelial cells, (ii) one of the recombinant viruses, R3616, was a γ34.5 deletion mutant and (iii) plaques are a sign that lytic infection had taken place, this disclosure implied that also in the natural host HSV γ34.5 mutants would infect and replicate in tumour cells other than those from neuronal tissue.

72.1 However, document D2 discloses on page 1265, in the last column that "[l]astly and more significantly, while the function of ICP34.5 is not known, it is not essential for growth in cells in culture. [...]. The failure to recover virus from CNS suggests that brain cells, unlike cells grown in culture, do not express genes whose products can substitute for γ34.5 gene product and complement the deletion mutants."

72.2 Thus, firstly, the document itself points to the difference between the replicative properties of the γ34.5 mutant virus in vitro and in vivo. Secondly, although document D2 was published in 1990, i.e. five years before the priority date, there is not - as concluded above in point 70 - a single hint in the prior art published in this period to use γ34.5 HSV mutants for the treatment of tumours other than those of the nervous system. Therefore, the board concludes that at the priority date of the patent the skilled person would not have drawn any consequences for an in vivo treatment from the known replication properties of γ34.5 mutants in cell culture. That this attitude may have changed later may be derived from document D16, published four years after the priority date of the patent. This document relates to the evaluation of an HSV mutant for the treatment of breast cancer. It is stated in the last sentence of the "Abstract" that "... *in vitro* testing may predict which tumors will be most responsive *in vivo*."

73. Thus, given the circumstances at the priority date of the patent in suit, in the board's view, the skilled person would have considered the general disclosure in document D4a and the statement in document D24 (see points 61 and 62 above) as a hypothesis which, due to the absence of a reasonable expectation of success, would not have motivated him/her to use HSV mutants having a non-functional γ34.5 gene for the treatment of malignant cells which do not originate in the central nervous system.

74. Therefore, the subject-matter of claim 1 and also that of dependent claims 2 to 10 is not obvious in the light

of a combination of document D3 with either of documents D4a or D24.

Claim 11

75. Claim 11 relates to use of a specific γ34.5 mutant HSV in the manufacture of a medicament for use in treating a melanoma cancer.

76. The board has concluded above that it was not obvious to use HSV γ34.5 mutants for the treatment of tumour cells other than those originating from the central nervous system. Given the non-obviousness of this general teaching, a fortiori, for the reasons above the use of a γ34.5 mutant virus for the treatment of a specific tumour cell, melanoma, is also not obvious. Consequently, the subject-matter of claim 11 and of dependent claims 12 and 13 is considered as involving an inventive step.

77. The requirements of Article 56 EPC are fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent as granted.

The Registrar: The Chair:

P. Cremona G. Alt