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Datasheet for the decision of 10 October 2006

Case Number: T 0665/05 - 3.3.08

Application Number: 93907093.4

Publication Number: 0675961

IPC: C12N 15/869

Language of the proceedings: EN

Title of invention:
Treatment of tumorigenic disease with a modified HSV

Patentee:
Arch Development Corporation

Opponent:
BIOVEX LIMITED

Headword:
modified HSV/ARCH

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

Keyword:
"Main request: added subject-matter - no; inventive step - no"
"Auxiliary request: added subject-matter - no; inventive step - yes"

Decisions cited:
T 0939/92, T 0338/97, T 0210/02, T 0893/02, T 1329/04

Catchword:
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Case Number: T 0665/05 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 10 October 2006

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 21 March 2005 concerning maintenance of European patent No. 0675961 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent EP-A-0 675 961 with the title "Treatment of tumorigenic disease with a modified HSV" was granted on the basis of the European patent application No. 93 907 093.4 with eight claims. Claim 1 read as follows:

"1. The use of a $\gamma_1$34.5 deficient strain of herpes simplex virus vector in the manufacture of a pharmaceutical composition for treating tumorigenic disease."

II. An opposition was filed under Article 100(a) to (c) EPC (lack of inventive step, insufficiency of disclosure, added subject-matter). The opposition division concluded that the claims of the main request then on file contained subject-matter which was not disclosed in the application as filed and maintained the patent on the basis of the first auxiliary request.

III. Both the patentee and the opponent filed appeals, paid the appeal fees and submitted statements of grounds of appeal. Appellant I's (the patentee's) statement of grounds of appeal was accompanied by a new main request and four auxiliary requests.

IV. Each appellant filed further submissions in response to the other's statement of grounds of appeal. Appellant I's submissions were accompanied by a main request and seven auxiliary requests to replace the requests on file.

V. Observations under Article 115 EPC were received from a third party.

VI. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal, indicating its preliminary, non binding-opinion.

VII. Both parties filed submissions in answer to this communication. Appellant II's (the opponent's) submissions were accompanied by four documents. Appellant I's submissions filed on 11 September 2006 were accompanied by a new main request, six auxiliary requests to replace the previous ones and an additional document. The sole claim of the **main request** read as follows:

"1. The use of a $\gamma_1$34.5 minus strain of herpes simplex virus 1 in the manufacture of a pharmaceutical composition for treating tumorigenic disease."

VIII. The third party filed further observations under Article 115 EPC.

IX. Appellant I filed a list of the documents on file.

X. Oral proceedings took place on 10 October 2006 whereby Appellant I withdrew all auxiliary requests except for auxiliary request IV which was re-named **first auxiliary request**. This request comprised one claim which read as follows:

"1. The use of a $\gamma_1$34.5 minus strain of herpes simplex virus 1 in the manufacture of a pharmaceutical

composition for treating tumorigenic disease in the CNS."

XI. The following documents are mentioned in this decision:

(1): Martuza, R. L. et al., Science, Vol. 252, pages 854 to 856, May 1991;

(2): Chou, J. et al., Science, Vol. 250, pages 1262 to 1266, 30 November 1990;

(3): Chou, J. and Roizman, B., J. of Cellular Biochemistry, Supplement, Vol. 16, part C, Abstract N 303, Keystone Symposia on Molecular and Cellular Biology, 21 February to 7 March 1992.

(16): Chambers, R. et al., Proc.Natl.Acad.Sci.USA, Vol. 92, pages 1411 to 1415, February 1995.

XII. Appellant I's submissions in writing and during oral proceedings may be summarized as follows:

Main and first auxiliary requests
Article 123(2) EPC; added subject-matter

The sentence on page 10, line 32 of the application as filed which disclosed the "$\gamma_1$34.5 **minus"** virus had to be read in conjunction with the immediately preceding sentence which made it unambiguous that the mutation was **in** the $\gamma_1$34.5 gene. On a plain reading of the paragraph, the $\gamma_1$34.5 minus mutant was, thus, a mutant which carried an alteration in this gene. This was also confirmed by the fact that it was the $\gamma_1$34.5 gene which was mutated in the two viruses described on pages 30

and 32. Any allegation that the claim could be interpreted as comprising the use of other mutants was unfounded.

Article 56 EPC; inventive step

The closest prior art was document (1) which taught that a herpes virus mutated in the thymidine kinase gene (tk^-) was capable of destroying human glioblastoma cells but would not replicate in non-dividing cells such as neurons, ie that it could be used as a therapeutic means against human glioma.

Starting from the closest prior art, the problem to be solved could be defined as finding an alternative means for eradicating tumors. The provided solution was the $\gamma_1$34.5 minus mutant.

The patent provided technical evidence that the $\gamma_1$34.5 minus mutant solved the above mentioned problem. On page 13, lines 6 and 7, it was disclosed that the mutant virus could be produced in tumor cells (SK-N SH cells). Production of viral progeny in cells meant destruction of the infected cells, particularly when considered in view of the common general knowledge referred to on page 3, line 42 that production of infectious progeny virus was invariably accompanied by host cell death. Furthermore, the data reported in Table 1 and para.[0061] showed that the virus was safe to use since it had little pathogenic effect on mice even when injected at high concentration. This data established the plausibility of the claimed invention.

The claimed use was not rendered obvious by the combination of the teachings of documents (1) and (2). Document (1) made no mention of the $\gamma_1$34.5 minus mutant and other mutants were known in the art which were prima facie suitable for use in therapy, such as polymerase mutants. Thus, the specific choice of the $\gamma_1$34.5 minus mutant was not obvious even if document (2) disclosed that it did not grow in normal neuronal cells. As for document (3), it mentioned that cellular protein synthesis stopped after infection of neuroblastoma cell lines by the $\gamma_1$34.5 minus mutant. Yet, this did not mean that the cells were killed. Thus, the combination of this teaching with that of document (1) also did not render obvious the destruction of tumors by the mutant virus.

Inventive step was to be acknowledged over the scope of the claim of the main request. The patent in suit provided no evidence that other tumors than brain tumors could **not** be treated by the mutant virus. On the contrary, it disclosed that the mutant virus did not replicate in normal cells but would do so in neuroblastoma cells. Otherwise stated, it disclosed that cells with tumorous properties would be killed whereas cells without such properties would not. Accordingly, it provided a realistic model of what would happen when a tumor was infected by the virus irrespective of which tumor it might be. Thus, the technical contribution to the art by the patent in suit was commensurate with the scope of the claim.

For these reasons, the subject-matter of the pending claim of the main and the auxiliary requests was inventive.

XIII. Appellant II's submissions in writing and during oral proceedings may be summarised as follows:

Main and auxiliary requests
Article 123(2) EPC; added subject-matter

Claim 1 of both requests was directed to the use of a $\gamma_1$34.5 **minus** virus, ie comprised viruses also carrying mutations outside of the $\gamma_1$34.5 gene. In contrast, the passage on page 10 of the application as filed, which Appellant I relied upon as a basis for claim 1, only disclosed a mutant virus with a **specific** mutation in the $\gamma_1$34.5 gene. Accordingly, the subject-matter of the claim extended beyond the content of the application as filed. The requirements of Article 123(2) EPC were not fulfilled.

Article 56 EPC; inventive step

It was agreed that document (1) was the closest prior art and that the problem to be solved could be defined as providing a means for destroying tumors which would be an alternative means to the tk^- mutant described in this document.

The alleged solution was the $\gamma_1$34.5 minus mutant and the first question which arose was whether or not it could be derived from the patent in suit that the $\gamma_1$34.5 minus mutant would be a bona fide solution to the above mentioned problem. Indeed, the case law (eg. T 1329/04 of 28 June 2005, T 893/02 of 26 May 2004 and T 210/02 of 1 October 2004) made it quite clear that, in order for an effect (here, the intended use) to be taken into

account in the assessment of inventive step, it had to be rendered plausible by the teaching of the patent.

Taking into account that the technical evidence provided in the patent did not go any further than that already available from the state of the art and, most importantly, that the only relevant example was not directed towards defining the behaviour of the $\gamma_1$34.5 minus mutant in tumorous neuronal cells but in normal neuronal cells, the conclusion had to be reached that the plausibility of the $\gamma_1$34.5 minus mutant being deleterious to brain tumors had not been established.

If the board came to the opposite conclusion, it remained that the claimed subject-matter (main and auxiliary requests) lacked inventive step over the combination of the teachings of document (1) with those of document (2). Indeed, after document (1) had provided the information that a likely herpes virus for fighting brain tumors should at the same time not replicate in normal neuronal cells and replicate in brain tumor cells, the $\gamma_1$34.5 minus mutant became an obvious alternative since document (2) taught that it was non-virulent to normal neuronal cells. It was just a matter of "try and see" what its behaviour would be in brain tumor cells of the kind disclosed in document (1). As for document (3), it was only a short abstract and the skilled person would not derive from the little information it contained that there might be any problems in using the $\gamma_1$34.5 minus mutant in the claimed manner.

Claim 1 of the main request covered the use of the $\gamma_1$34.5 minus mutant for fighting tumors irrespective of

type. Its scope was, thus, extremely large. In contrast, the patent in suit did not provide any technical evidence even as regard the ability of the mutant to destroy brain tumor cells. Furthermore, even if this mutant did destroy brain tumor cells, this would not necessarily imply that it would also work in other tumors. Therefore, the alleged technical effect on which inventive step relied had not been established over the scope of the claim and the scope of the claim was not commensurate with the technical contribution allegedly imparting inventive step. In accordance with the case law (eg. T 939/92 of 12 September 1995 and T 338/97 of 7 February 2000), these were two reasons why inventive step could not be acknowledged.

XIV. Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed on 11 September 2006 or the first auxiliary request filed during the oral proceedings.

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

Reasons for the decision:

Main and auxiliary requests

Articles 123(2)(3) EPC and 84 EPC

1. On pages 10 and 11 of the application as filed, the following statement is found:

"..., use of the HSV-1 virus with a specific mutation in the $\gamma_1$34.5 gene provides a method of therapeutic treatment of tumorogenic diseases both in the CNS and in all other parts of the body. The "$\gamma_1$34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread. Therefore, given the ability to target tumors within the CNS, the $\gamma_1$34.5 minus virus has proven a powerful therapeutic agent for hitherto virtually untreatable forms of CNS cancer."

This passage undoubtedly provides a basis for claiming a composition for treating tumorigenic diseases in general (claim of the main request) and of the central nervous system (claim of the first auxiliary request). It fails to mention that the "$\gamma_1$34.5 minus virus" is a viral **strain** and the word "strain" is not used anywhere else in the application. It is the board's understanding that the term "strain" is used to define a population of viruses which is genetically homogeneous. Thus, the use of this term in the claim of each request does not bring any information over that contained within the term $\gamma_1$34.5 minus virus.

2. At oral proceedings, it was argued that the term "$\gamma_1$34.5 **minus**" included other mutants than those arising from an alteration in the $\gamma_1$34.5 gene and, that, therefore, the claim did not fulfil the requirements of Article 123(2) EPC. The board does not find this argument convincing because, as can be seen from the above-mentioned paragraph, the HSV-1 mutant is also defined as "with a specific mutation **in** the $\gamma_1$34.5 gene", making it quite clear that the mutation has to be **in** this gene. Appellant II's interpretation of the term

$\gamma_1$34.5 minus and the objection derived therefrom are, thus, unfounded.

3. The differences between granted claim 1 and claim 1 of the main and auxiliary requests which are relevant pursuant to Article 123(3) EPC are, firstly, that in the granted claim the $\gamma_1$34.5 strain is qualified as being "deficient" rather than "minus" and, secondly, that the herpes simplex virus is qualified as a vector. According to the Concise Oxford English Dictionary (tenth Edition), the definition of the word "deficient" is "not having enough of a specified quality", that of the word "minus" is "lacking". The use of the word "minus" in the present claim of each request, thus, amounts to a restriction of the scope of the claim insofar as it does not anymore include the use of mutants producing "some" $\gamma_1$34.5 protein (less than the wild-type virus/altered protein). The deletion of the word "vector" does not change the scope of the claim because, within the framework of the invention, the $\gamma_1$34.5 minus mutant virus brings the same information into the cells (lack of $\gamma_1$34.5 protein), whether or not it be called a vector.

4. The amendments to the claim do not introduce a lack of clarity nor do they alter the claimed subject-matter in such a way that it would require additional support from the description.

5. The requirements of Articles 123(2)(3) and 84 EPC are fulfilled.

Article 56 EPC; inventive step

6. The closest prior art is document (1) which is concerned with establishing an experimental therapy of human glioma by means of a thymidine kinase-negative mutant of herpes virus simplex 1 (tk^- HSV-1). This mutant is severely impaired for replication in non-dividing cells and for replication in the mammalian nervous system. Yet, it destroys the glioma tumorous cell line U87 even when inoculated at low concentration (page 854, left-hand and middle columns). Tumors which have been induced in mice become smaller when treated by injection of the mutant virus (passage bridging page 854 and 855 to the middle-column). The authors conclude with the following statement:

"Our study suggests that genetically altered viruses are worthy of further exploration as a means of therapy for some tumors, such as malignant human gliomas, that are resistant to currently available treatments."

7. Starting from the closest prior art, the problem to be solved can be defined as providing an alternative means to the tk^- HVS-1 mutant for the treatment of malignant tumors. The formulation of this problem does not per se contribute to inventive step because of the above mentioned suggestion in document (1).

8. The provided solution is another HSV-1 mutant, the $\gamma_1$34.5 minus mutant.

9. This mutant was known in the prior art from documents (2) and (3), the two documents originating from the same research group. While clearly different from those

described in document (1), the experimental systems used in these two studies nonetheless allow a comparison between the $\gamma_1$34.5 minus and the tk$^-$ mutants as regards the properties which led the authors of document (1) to suggest the use of the tk$^-$ mutant in the therapy of malignant tumors, namely, its absence of replication in non-dividing cells and in the mammalian nervous system, and its active replication in a brain tumor cell line or brain tumors (see point 6, supra). Both documents will, thus, be taken into consideration.

10. Document (2) teaches that the majority of mice which receive an intracerebral inoculation of the $\gamma_1$34.5 minus mutant survive (passage bridging pages 1264 and 1265). This, of course, is an analogous finding to that reported in document (1) that the tk$^-$ mutant is impaired for replication in the mammalian nervous system. The $\gamma_1$34.5 minus mutant sharing with the tk$^-$ mutant "half of the characteristics" needed for use against malignant tumors, it would prima facie appear as a promising candidate for an alternative to the tk$^-$ mutant.

11. Document (3) reports that neuroblastoma cells infected with the **wild-type** $\gamma_1$34.5 virus experience stress which causes them to cease all protein synthesis and that the function of the wild-type $\gamma_1$34.5 gene is to preclude the cessation of protein synthesis. This is demonstrated by an experiment where the events which occur after infection of a neuroblastoma cell line with the wild-type virus are compared with those occurring after infection with the $\gamma_1$34.5 minus mutant. It is, thus, reported:

"... we discovered that a neuroblastoma cell lines *[sic]* of human neuronal origin replicated wild type virus but that cells infected with the $\gamma_1$34.5 minus mutant ceased all protein synthesis between 7 and 12 hours post infection even though viral DNA was made and mRNA accumulated in these cells."

Document (3), thus, teaches that, contrary to what happens with the tk^- mutant in glioma cells, the inoculation of a neuroblastoma cell line - ie of a cell line of tumorous origin - with the $\gamma_1$34.5 minus mutant does not lead to the production of viral particles. Production of viral particles is the very mechanism which accounts for the tumor cells dying when they are infected by the tk^- mutant. The data presented in document (3), thus, mean that the $\gamma_1$34.5 minus mutant most significantly differs from the tk^- mutant in the very feature which is indispensable for treating brain tumors, namely the ability to destroy tumor cells. This fact would not have immediately prompted the skilled person to propose it as a possible alternative to the tk^- mutant of document (1).

12. In the board's judgment, the realisation by the present inventors that the specific effect caused by the absence of the $\gamma_1$34.5 protein - cessation of protein synthesis - could, like viral multiplication, be taken advantage of to elaborate a treatment of brain tumorigenic diseases required inventive step.

13. Example I is the only example provided by the patent in suit to illustrate the claimed use of the $\gamma_1$34.5 minus mutant for treating tumorigenic diseases. It corresponds to the technical teaching disclosed in

document (3): under the heading "HSV-1 recombinant viruses lacking the $\gamma_1$34.5 gene induce the shut off protein synthesis in neuroblastoma cells", it is disclosed that the neuroblastoma cell line SK-N SH produces 100 fold less mutant viruses than a fully permissive cell line. It is fair to say that the actual experimental contribution to the art by the patent in suit is very small, the extra information provided as compared to that in document (3) being the identification of a neuroblastoma cell line (SK-N SH) and the quantitative effect which the cessation of protein synthesis has on the number of viral particles produced.

14. Appellant II argued that in the absence of any meaningful technical contribution in the patent in suit, it was not plausible that the invention was a solution to the problem to be solved and, relying on such case law as T 1329/04, T 893/02 and T 212/02 (supra), concluded therefrom that inventive step should not be acknowledged.

15. The case dealt with in T 1329/04 concerned an hitherto unknown protein named GDF-9, the patentability of which was argued on the basis that it was a new member of the TGF-β superfamily. GDF-9 did not exhibit all of the structural features shared by the proteins of this family and it could not be attributed to any of the subgroups in the family on the basis of sequence homology (points 7 and 8 of the decision). No data were available which might have served to back up the assertion that GDF-9 would play any one of such roles as were known to be fulfilled by TGF-β family members. The then competent board indicated (point 3 of the

Reasons) that it would have been prepared to accept that the protein belonged to the TGF-β superfamily even in the absence of any functional evidence, if the compound had exhibited the relevant structural features and so, because, in the prior art, it had already been accepted on this basis that another compound, GDF-1, was a member of the TGF-β superfamily. Conversely, as the pending application did not provide any satisfactory evidence to this effect, the board concluded that GDF-9 had not been demonstrated to be a bona fide solution to the problem to be solved and, thus, rejected the application for failing to fulfil the requirements of Article 56 EPC.

16. There is a fundamental difference between this earlier case and the present one, namely that since the then claimed compound had not been described in the prior art, the plausibility of it being what was claimed **must entirely rely** on evidence provided in the application. In contrast, in the present case, the skilled person knew of the $\gamma_1$34.5 minus mutant from the prior art and, in particular, that its inoculation in a cell line of tumoral origin induced cessation of protein synthesis, this mechanism being confirmed and somewhat extended in the patent in suit.

17. Thus, once it has been realized - and this required inventive step (points 6 to 12, supra)- that the $\gamma_1$34.5 minus mutant can be used for fighting brain tumors, it becomes plausible on the basis of the disclosure in the prior art and in Example 1 of the patent in suit that the mutant is an alternative solution to the problem of fighting tumors in the central nervous system. Otherwise stated, the plausibility issue which arose

with in T 1329/04 simply does not arise in the present case.

18. In the cases dealt with in T 893/02 and T 212/02 (supra) inventive step was denied because there existed no evidence at the filing/priority date that the claimed subject-matter had the properties it was claimed for. These two cases are no more relevant than the case dealt with in T 1329/04 (supra) and for the same reasons.

19. In the present case, inventive step comes from the fact that non-obvious consequences were drawn from a specific effect **and** concerning this effect. For this reason, it can only be acknowledged in relation to it. At the filing/priority date, there was no evidence as to the effect the $\gamma_1$34.5 minus mutant may have on other types of tumor cells than brain tumor cells. In addition, the mutant is expected to grow in replicating normal cells (patent in suit, page 12, par.[64]), a feature which is certainly not favourable to making the treatment specific to tumor cells. The potential usefulness of the $\gamma_1$34.5 minus mutant for **treating tumors in general** remains a mere assumption.

20. In accordance with the principles expressed in the case law (eg. T 939/92 and T 338/97 supra) that a technical effect which justifies acknowledging inventive step must be present "over the scope of the claim" and that there must be a balance between the technical contribution to the art made by the invention and the scope of the claim, the conclusion is reached that the claim of the main request which encompasses the use of the $\gamma_1$34.5 mutant for the manufacture of a medicament

for treating tumorigenic diseases in general does not fulfil the requirements of Article 56 EPC whereas the claim of the first auxiliary request which is limited to the treatment of the tumors in the central nervous system does.

21. During oral proceedings, Appellant II also argued that the neuroblastoma cell line, SK-N SH, was to be regarded as representative of normal neuronal cells rather than of tumorous cells. Thus, in its opinion, the patent in suit provided no evidence of the fate of the $\gamma_1$34.5 minus mutant in tumor cells which, in turn, meant that the plausibility of its use for treatment had not been established. The board is aware from some of the post-published evidence (eg. document (16)) that the SK-N SH cell line turned out to "answer" to inoculation by the $\gamma_1$34.5 minus mutant in a way which was closer to that of normal neuronal cells than to that of tumor cells (eg. glioma). Yet, there is no prior art to this point. And, in this context, it must be remembered that inventive step has to be assessed from the point of view of the skilled person at the filing/priority date of the patent. At that date, in the absence of any indication to the contrary, he/she had no reason to doubt that the SK-N SH neuroblastoma cell line was a cell line of tumoral origin which was representative of tumor cell lines. The reasoning which leads the board to acknowledge inventive step of the claim of the first auxiliary request is, thus, not affected by this later published development.

22. Appellant I put forward as argument for allowing the claim of the main request that the neuroblastoma cell line SK-N SH constituted a model representative of all

tumor cells as the patent in suit showed that the cell line allowed replication of the $\gamma_1$34.5 minus mutant and that this mutant would not be expected to grow in any other cells than tumor cells. In this context, reference was made to the patent in suit, page 13:

"... The SK-N SH neuroblastoma cell lines produced 100 fold less mutant viruses than the fully permissive Vero cells "

and to Table 1 together with paragraph [0061] which showed that mice receiving an intercerebral inoculation of the virus did not die. In its view, this last result meant that non-neuronal, normal brain cells were not killed by the virus, which, in turn, implied that normal cells in general would not be killed.

23. For the board, producing the viral mutant in SK-N SH cells with a 100 fold less efficiency than might be achieved under "normal circumstances" does not render credible that viral particles will be produced in tumor cells in general to such an amount that the cells will be destroyed. As for the lack of sensitivity to the mutant virus of normal cells, in general, which is alleged on the basis of an in vivo experiment carried out in mice, it is contradicted by the patent in suit itself on page 12, paragraph [0064] (see point 19, supra). For these reasons, the arguments are not considered relevant.

24. The main request is rejected for failing to fulfil the requirements of Article 56 EPC. Inventive step is acknowledged to the first auxiliary request.

First auxiliary request

Article 83 EPC, sufficiency of disclosure

25. In the written part of the proceedings, the argument was brought up that the subject-matter of a claim corresponding to the claim of the present main request could not be worked over the whole area claimed. This objection is not relevant as regard the subject-matter of the claim of the first auxiliary request which is limited to the use of the $\gamma_1$34.5 minus mutant in the manufacture of a pharmaceutical composition for treating malignant diseases in the CNS. At oral proceedings, Appellant II indicated that it had no objections to the claim of the first auxiliary request other than that of added subject-matter and lack of inventive step. For these reasons, the board does not see that the matter should be pursued any further.

Order:

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the claim of the first auxiliary request filed during oral proceedings and a description and drawings to be adapted thereto.

The Registrar The Chairman

A. Wolinski L. Galligani