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Datasheet for the decision of 10 November 2010

Case Number: T 1364/08 - 3.3.04

Application Number: 00974225.5

Publication Number: 1227828

IPC: A61K 35/76

Language of the proceedings: EN

Title of invention:
Viruses for the treatment of cellular proliferative disorders

Applicant:
Oncolytics Biotech Inc.

Headword:
Cellular proliferative disorders/ONCOLYTICS

Relevant legal provisions:
EPC Art. 56, 83

Relevant legal provisions (EPC 1973):
-

Keyword:
"Sufficiency of disclosure - (yes)"
"Inventive step - (no)"

Decisions cited:
T 0609/02

Catchword:
-

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Case Number: T 1364/08 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 10 November 2010

Appellant: Oncolytics Biotech Inc.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 11 February 2008 refusing European patent application No. 00974225.5 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: M. Wieser
G. Alt

Summary of Facts and Submissions

I. The appeal was lodged by the Applicant (Appellant) against the decision of the Examining Division to refuse under Article 97(2) EPC the patent application EP 00 974 225.5 (published as WO 01/35 970), having the title: "Viruses for the treatment of cellular proliferative disorders".

II. The Examining Division decided that the only request before it, claims 1, 2, 4 to 49 filed a with letter dated 18 December 2007 and claim 3 filed during oral proceedings on 17 January 2008, did not meet the requirements of Articles 56 and 83 EPC.

III. The Board expressed its preliminary opinion in two communications dated 18 May 2010 and 28 October 2010 respectively.

Oral proceedings were held on 10 November 2010.

IV. The Appellant requested that the decision under appeal be set aside and a patent be granted on the basis of claims 1 to 49 submitted with its letter dated 9 September 2010. These claims were identical to the claims before the Examining Division.

V. Claim 1 of the Appellant's request reads as follows:

"An adenovirus in which the VAI gene is lacking or mutated and which is capable of replicating in cells having an activated Ras-pathway but not in normal cells for treating a Ras-mediated cell proliferative disorder in a mammal, whereby the adenovirus is to be

administered to proliferating cells in a mammal having a Ras-activated pathway under conditions which result in substantial lysis of the proliferating cells or for treating a neoplasm suspected of having an activated Ras-pathway in a mammal, wherein after the surgical removal of substantially all of the neoplasm the adenovirus is to be administered to the surgical site in an amount sufficient to result in substantial oncolysis of any remaining neoplasm."

Dependent claims 2 to 26 and 28 to 49 refer to preferred embodiments of the adenovirus of claim 1, claim 27 refers to an in vitro method for treating a population of cells using the adenovirus of claim 1.

VI. The following documents are referred to in this decision:

(7) Journal of Virology, vol.69, no.7, 1995, pages 4299 to 4307

(8) WO 99/08 692

(14) WO 96/00 007

(16) The EMBO Journal, vol.17, no.2, 1998, pages 3351 to 3362

(20) Cell, vol.31, 1982, pages 543 to 551

(21) The EMBO Journal, vol.6, no.3, 1987, pages 689 to 697

(T1) Cancer Research, vol.63, 2003, pages 5544 to 5550

VII. The submissions made by the Appellant, as far as they are relevant to the present decision, may be summarised as follows:

Based on what was described in the application as filed and taking into account what was known in the art so far as oncolytic reovirus was concerned, it was credible that the modified adenovirus specified in claim 1 would have been effective for the treatment of Ras-mediated cell proliferative disorder. This therapeutic efficacy was backed up by post-published evidence in the form of document (T1).

Should the Board come to a negative decision on this issue, it was intended to request the referral of questions to the Enlarged Board of Appeal according to Article 112 EPC as there seemed to exist a "discrepancy between case law of the Boards of Appeal" as regards the admissibility of post-published documents as evidence for sufficiency of disclosure.

The subject-matter of claim 1 was not obvious in the light of the cited prior art documents.

Document (14) described methods for killing tumour cells by using a mutated Herpes Simplex Virus (HSV). The document, generally disclosing the treatment of tumour cells of various different types, did not refer to the specific treatment of a neoplasm having an activated Ras-pathway in which the dsRNA-mediated activation of protein kinase R (PKR) was blocked at the level of autophosphorylation.

The closest prior art was represented by document (8), or equally document (16), which disclosed the treatment of Ras-mediated neoplasm by using a reovirus. The problem underlying the present invention was, as defined by the Examining Division, "the provision of means other than use of reovirus to achieve lysis of cells having an activated Ras-pathway, and not of normal (that is, not Ras activated pathway) cells". Neither document (8) nor document (16) itself contained any hint to replace the reovirus disclosed therein by a mutated adenovirus, nor did document (7) (or documents (20) and (21)), referring to such mutated adenovirus, contain any suggestion that would encourage a skilled person to use this virus in a method for treating a neoplasm suspected of having an activated Ras-pathway.

The skilled person, knowing that reoviruses differed drastically from adenoviruses, would not have considered replacing the reovirus of documents (8) or (16) by an adenovirus as disclosed in documents (7), (20) and (21).

Accordingly, the requirements of Article 56 EPC were met.

Reasons for the decision

Sufficiency of disclosure - Article 83 EPC

1. "Genetic alteration of the proto-oncogen Ras is believed to contribute to approximately 30% of all human tumours. The role that Ras plays in the pathogenesis of human tumours is specific to the type

of tumour" (quoted from page 3, lines 14 to 16 of the application).

2. Protein kinase R (PKR), is an interferon-induced, double-stranded (ds) RNA-activated protein kinase which protects cells against viral infections.

In situations of viral infection, the dsRNA created by viral replication binds to the N-terminal domain of PKR and thus activates it. Once active, PKR is able to phosphorylate the translation initiation factor eIF2a. This inhibits further cellular mRNA translation, thereby also preventing viral protein synthesis such that viral replication and thus also cell lysis is prevented.

3. Claim 1 refers to an adenovirus in which the VAI gene is lacking or mutated and which is capable of replicating in cells having an activated Ras-pathway but not in normal cells for treating a Ras-mediated cell proliferative disorder in a mammal.

4. It has been established by case law that for a claim referring to a therapeutic application of a substance or composition, it is a requirement according to Article 83 EPC that it is demonstrated that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease to be treated. This mechanism can be either known from **the prior art**, or be shown in **the application** per se, for example by the provision of experimental tests. Once this evidence is available, post-published evidence may be taken into account to back up these findings (see decision T 609/02 of 27 October 2004, point 9 of the reasons).

5. The application does not provide any experimental data proving that an adenovirus of claim 1 is able to replicate in cells having an activated Ras-pathway but not in normal cells. No data is present demonstrating that such a virus can be useful for the treatment of Ras-mediated cell proliferative disorders.

6. However, on pages 3 to 6 the application as published contains a detailed summary of the "state of the art".

Reference is made to document (16) of the list of documents given on pages 1 and 2 of the application, which is also document (16) in the present case. Page 5, lines 7 to 8 of the present application read: "It has been demonstrated that in Ras transformed cells, dsRNA-mediated activation of PKR was blocked at the level of autophosphorylation."

Document (16) itself moreover discloses that reoviruses, being dsRNA viruses, in their wild-type form lack an effective PKR counteracting mechanism. They cannot therefore replicate in normal cells but only in cells having an activated Ras pathway because downstream effectors of Ras inactivate PKR. This makes them a useful tool for the treatment of Ras-mediated cell proliferative disorders. This is also disclosed in document (8), a published International patent application whose inventors and applicants are the authors of document (16). On page 6, lines 12 to 13 it is stated that reoviruses use the host cell's Ras pathway machinery to down-regulate PKR and thus reproduce. Claim 1 of document (8) reads: "Use of

reovirus for the manufacture of a medicament for treating Ras-mediated neoplasm in a mammal."

7. It was known that, contrary to reoviruses, various other viruses have evolved PKR inhibitory functions as a mechanism of defence against the host's antiviral response in order to counteract viral replication restrictions. This is acknowledged on page 4, line 15 to page 5, line 5 of the application as published where the different "strategies" of four viruses to inhibit PKR activation in response to their presence are described.

8. On page 4, lines 18 to 23 it is said that adenovirus produces large amounts of VAI RNA which inactivates PKR by acting as a competitive inhibitor of the full length viral dsRNA. PKR bound to VAI RNA is not activated. Reference is made to document (8) of the application's own reference list, which is document (21) in the present case. In the section "Materials and Methods" under "Cells and virus" on page 696, left column, the authors of document (21) mention that the used adenovirus mutant has been described previously and was provided to them by the authors of a prior art document which is document (20) in the present case. A further document on file, published by the authors of document (20), is document (7), which reports that a significant number of adenoviruses, in which the VAI gene has been mutated, lost their ability to counteract the cellular antiviral response mediated by the interferon-induced, dsRNA-activated protein kinase PKR (abstract), which made them unable to replicate in normal cells.

9. Besides the description of the viral anti-PKR strategies of Vaccinia virus and of Parapoxvirus, the present application, on page 5, lines 1 to 3, describes also that the Herpes simplex virus (HSV) infected cell protein 34.5 (ICP34.5) encoded by the $_{\gamma}$34.5 gene of HSV prevents the antiviral effects exerted by PKR. On page 6, lines 10 to 13 the application refers to document (32) of its own reference list (which is document (14) in the present case), by saying that it "generically describes methods for selectively killing neoplastic cells which utilize altered viruses that are capable of replication in neoplastic cells while sparing surrounding normal tissue". Document (14) refers to the use of a HSV mutant that is incapable of expressing a functional $_{\gamma}$34.5 gene product (see claim 1).

10. The Board is of the opinion that the disclosure in the prior art is such that it is plausible that the adenovirus of claim 1 is useful for the therapeutic application referred to in the claim. Under these circumstances the disclosure in post-published document (T1) can be taken into account to back up these findings. In fact, document (T1) contains experimental data demonstrating that an adenovirus in which the VAI gene is lacking or mutated can be used for oncolytic virotherapy of Ras-mediated cell proliferative disorders such as pancreatic tumours (see section "Results", starting on page 5545, right column).

Therefore the application is considered to disclose the invention in a manner sufficiently clear and complete to be carried out by a person skilled in the art as required by Article 83 EPC.

Inventive step - Article 56 EPC

11. Documents (8) and (16) refer to the same subject-matter and are authored by the same group of persons. While document (16) is a scientific publication, document (8) is a published International patent application which in addition refers to the therapeutic application of the scientific findings disclosed in document (16) (see claims, page 6, first full paragraph and examples 3, 4 and 11 of document (8)).

For these reasons, the Board considers document (8) to represent the closest state of the art for the assessment of inventive step.

12. In agreement with the Examining Division the Board sees the problem to be solved by the application in the provision of means, other than reovirus, to achieve lysis of cells having an activated Ras-pathway, but not of normal cells.

13. For the solution of this problem, the application suggests the use of adenovirus in which the VAI gene is lacking or mutated.

The Board, also in consideration of what has been said in points (1) to (7) above with regard to Article 83 EPC, comes to the conclusion that the underlying problem has indeed been solved by the claimed subject-matter.

14. It remains to be examined if the solution claimed is obvious in the light of the prior art on file.

The skilled person is aware of the fact that in several different viruses, including adenovirus, genes have been identified which encode products responsible for the inactivation of PKR in host cells (see points (4) to (6) above).

Document (7) discloses adenoviruses in which the VAI gene is mutated and reports that a significant number of these mutants lost their ability to counteract the cellular antiviral response mediated by PKR (see point (8) above). Thus these cells, like wild-type reovirus which lacks any PKR counteracting activity, are unable to replicate in normal cells.

15. The Appellant has put forward several arguments why a skilled person would not have considered amending the teaching in the closest prior art document (8) by replacing the wild-type reovirus disclosed therein with the adenovirus mutant of document (7).

None of the two documents contained any hint that would encourage the skilled person to do so.

Beyond that, knowing that reoviruses, whose genome consisted of dsRNA, a strong PKR activator, differed drastically from adenoviruses which were DNA viruses with nuclear replication, the skilled person would not have considered replacing the reovirus of document (8) by an adenovirus as disclosed in document (7).

Although VAI-deficient adenovirus mutants had been described in the prior art, it could not be expected that their deficiency to inhibit PKR activation would

be complemented in cells having an activated Ras-pathway, in the same way as reoviruses which were Ras-dependent in their wild-type form.

16. In accordance with the case law of the boards of appeal, the subject-matter of a claim is considered obvious within the meaning of Article 56 EPC, if it is the result of an obvious course of action, i.e. one which the skilled person would have carried out in expectation of achieving the result. In other words, obviousness is found not only when the results are clearly predictable but also when there is a reasonable expectation of success.

A reasonable expectation of success should not be confused with the understandable "hope to succeed". Rather it implies the ability of the skilled person to predict rationally, on the basis of the knowledge existing before a research project is started, the successful conclusion of the project within acceptable time limits.

Inventive step was denied by the Boards of Appeal in several cases because the skilled person was in a "try and see" situation: if the skilled person, in view of the teaching in the prior art, had already clearly envisaged a group of compounds and then determined by routine tests whether such compounds had the desired effect (cf. Case Law of the Boards of Appeal of the EPO, 6th edition 2010, chapter I.D.6).

17. In the present case the skilled person looking for means, other than reovirus, for oncolytic virotherapy, knows from the teaching in the prior art of the

existence of a limited number of mutated viruses which, due to their deficiency to inhibit PKR activation, are unable to replicate in normal cells. He/she also knows that for wild-type reoviruses, which also are incapable of inhibiting PKR, this deficiency is complemented in cells having an activated Ras-pathway.

Although the skilled person definitely is aware that reoviruses and adenoviruses are different in many aspects as highlighted by the Appellant, the Board is of the opinion that he/she, when aiming to solve the problem underlying the present application, would have envisaged the mutated adenovirus disclosed in document (7) (and in documents (20) and (21)). This is so, firstly, because he/she would have realized that the relevant mechanism - complementation of lacking PKR inhibition by a compound of the Ras-pathway - is the same for both reoviruses and mutated adenoviruses, and secondly, because the mutated adenovirus disclosed in document (7) (and in documents (20) and (21)) "was the only mutant within the VAI gene which was available" (see Appellant's letter of 19 June 2008, page 4, item 2.4, first paragraph). Thus, the skilled person was in a "try and see" situation and would have determined by routine tests whether this virus has the desired effect to make it a useful tool for the treatment of Ras-mediated cell proliferative disorders. By doing so he/she would have arrived at the subject-matter of claim 1 in an obvious way.

18. Therefore, the subject-matter of claim 1 is not considered to involve an inventive step and does not therefore meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith