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D E C I S I O N
of 16 February 2006

Case Number: T 0036/04 - 3.3.04

Application Number: 95917100.0

Publication Number: 0760675

IPC: A61K 38/17

Language of the proceedings: EN

Title of invention:

Compositions comprising DNA damaging agents and p53

Patentee:

THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

Opponent:

SCHERING-PLOUGH CORPORATION

Headword:

DNA damaging agents and p53/UNIVERSITY OF TEXAS

Relevant legal provisions:

EPC Art. 52(4), 54, 56, 83

Keyword:

"Not patentable invention (no)"

"Novelty, inventive step, sufficiency of disclosure (yes)"

Decisions cited:

G 0005/83, T 0181/82, T 0464/94, T 0936/96, T 1020/03

Catchword:

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Case Number: T 0036/04 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 16 February 2006

Appellant I: THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
11 November 2003 concerning maintenance of
European patent No. 0760675 in amended form.

Composition of the Board:

Chair: M. Wieser
Members: B. Claes
G. Weiss

Summary of Facts and Submissions

- I. Appeals were lodged by the Patent Proprietor (Appellant I) and by the Opponent (Appellant II) against the decision of the Opposition Division whereby European patent No. 0 760 675 was maintained in amended form pursuant to Article 102(3) EPC.
- II. The patent had been opposed under Article 100(a) EPC for lack of novelty (Article 54 EPC), for lack of inventive step (Article 56 EPC) and because it did not relate to a patentable invention according to Article 52(4) EPC, under Article 100(b) EPC on the ground of lack of sufficient disclosure and under Article 100(c) EPC on the ground of added subject-matter.
- III. The Opposition Division had decided that the claims of the main request before them were not novel according to the requirements of Article 54 EPC, and that the claims of the first auxiliary request did not involve an inventive step as required by Article 56 EPC. However, they decided that claims 1 to 18 of the second auxiliary request before them met all requirements of the EPC.
- IV. The Board expressed their preliminary opinion in a communication dated 29 August 2005. Oral proceedings were held on 16 February 2006.

Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 5 of the new main request filed at the oral proceedings.

Appellants II requested that the decision under appeal be set aside and that the European patent No. 0 760 675 be revoked.

V. Independent claims 1 and 4 of Appellant's I new main request read as follows:

"1. Use of a p53 protein or gene and DNA damaging compound in a pharmacologically acceptable form for the preparation of a medicament to kill tumor cells which are located within an animal, wherein the animal is first exposed to the DNA damaging compound and then contacted with a p53 protein or gene, wherein the tumor is contacted with a DNA damaging compound by administering to the animal a therapeutically effective amount of a pharmaceutical composition comprising a DNA damaging compound.

4. Use of a p53 protein or gene in a pharmaceutically acceptable form for the preparation of a medicament to kill tumor cells which are located within an animal, wherein the medicament is administered in combination with a DNA damaging agent selected from the group consisting of X-ray radiation, UV-radiation, γ -irradiation or microwaves, wherein the tumor is first exposed to the DNA damaging agent and then contacted with the p53 protein or gene."

Claims 2 and 5, dependent on claims 1 and 4 respectively, refer to a preferred mode of administration of a p53 gene. Dependent claim 3 relates to a group of preferred DNA damaging compounds.

VI. The present decision refers to the following documents:

- (1) Proceedings of the American Association of Cancer Research; vol. 35, March 1994, pages 692 to 693
- (2) Cell, vol. 74, 1993, pages 957 to 967
- (7) Nature, vol. 362, 1993, pages 847 to 849
- (14) The Journal of Thoracic and Cardiovascular Surgery; vol. 112, No. 5, November 1996, pages 1372 to 1377

Document (14) was originally filed by Appellant I as Annex (2) to document (14), a declaration of Dr K.B. Menander. Nevertheless, in the present decision it will be referred to as document (14).

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

Claims 1 to 5 had a basis in the application as originally filed. Claim 4 referred to a second or further medical use of a substance which was known *per se* and took the form accepted by the Enlarged Board of Appeal in decision G 5/83 (OJ EPO 1985, 64). According to established case law of the Boards of Appeal it did not contravene the requirements of Article 52(4) EPC.

Neither document (1), nor documents (2) or (7) disclosed the order of administration as contained in independent claims 1 and 4, i.e. first the DNA damaging compound or agent, then a p53 protein or gene.

Appellant II had not substantiated the argument that a skilled person could not carry out the invention over the whole scope claimed.

The chronological order of administration of the two compounds of the medicament prepared according to claim 1, namely first the DNA damaging compound or agent then a p53 protein or gene, was disclosed in claim 13 of the application as filed. In this situation it was permissible and in line with the case law of the Boards of Appeal to consider post published evidence, like document (14), to back up the findings in the patent application. Therefore, starting from document (1), representing the closest state of the art, the problem underlying the invention was to provide an improved method to kill tumor cells. The solution to this problem according to claims 1 to 5 could not have been derived from the relevant prior art in an obvious way.

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

Claim 4 referred to the use of p53 protein or gene for the preparation of a medicament. The intended use of the p53 containing medicament, namely to kill tumor cells, was known from the relevant prior art. The feature distinguishing the subject-matter of claim 4 from the prior art, namely the administration of the medicament to tumor cells after they have been exposed to DNA damaging irradiation, was considered to refer to

a method of therapy which was not patentable according to Article 52(4) EPC.

The disclosure in document (1), which came very close to the subject-matter of the claims, was detrimental to their novelty.

The claims, not being restricted to the treatment of p53 deficient tumor cells, were too broad to enable a skilled person to carry out the invention over the whole scope without undue burden.

Document (1) was considered to represent the closest state of the art for the assessment of inventive step. The problem to be solved in the light of this prior art was seen in the provision of an alternative method to kill tumor cells. In the light of the disclosure in document (1), taken alone or in combination with documents (2) or (7), no inventive activity was required to expose the tumor cells first to a DNA damaging compound or agent and then to contact them with a p53 protein or gene.

The application as filed did not contain experiments or data showing a surprising or beneficial effect of any specific chronological order of administration of the pharmacologically active ingredients. On the contrary, it explicitly stated that the order was not critical. Post published document (14), which was the first publication containing experimental data showing an improved anti-tumor effect dependent on the chronological order of administration of first the DNA damaging compound cisplatin and then a p53 gene, could

not be used as evidence for the involvement of an inventive step.

Reasons for the Decision:

Amendments, Clarity - Articles 123(2), 123(3) and 84 EPC

1. Claim 1 of the new main request is based on claims 1, 13, 16 and 30 as originally filed, claim 2 of the new main request is based on original claim 28 and claim 3 of the new main request on claim 2 and page 28, lines 23 to 25 of the application as filed. Claim 4 of the new main request finds a basis in original claims 1, 13, 26 and 29, and claim 5 of the new main request in original claim 28.

The claims have not been amended during opposition proceedings in such a way as to extend the protection conferred; they are clear and concise and supported by the description.

Claims 1 to 5 meet the requirements of Articles 84, 123(2) and 123(3) EPC.

Patentable inventions - Article 52(4) EPC

2. Claim 4 is drafted as referring to a second (or further) medical use of a p53 protein or gene.

Appellant II argued that the use of a p53 protein or gene in cancer therapy was already known in the art. A claim referring to the use of this known compound for a known purpose, which claim was further characterised by

a step of irradiation treatment, was excluded from patentability by virtue of Article 52(4) EPC.

3. According to the decision of the Enlarged Board of Appeal G 5/83 (OJ EPO 1985, 64) a claim which takes the form of use of a composition for the preparation of a medicament for a specific therapeutic use, will avoid being in conflict with Article 52(4) EPC, irrespective of the degree of detail with which the therapeutic use is stated (cf. decision T 1020/03 of 29 October 2004, point (18) of the reasons).

If the subject-matter of a claim avoids the prohibited method of therapy of Article 52(4) EPC first sentence, as in the Board's judgement is the case for present claim 4 which is in the approved "Swiss" form, compliance with this provision does not need to be considered further. The decisive question to be answered in accordance with decision G 5/83 is then whether the intended method of treatment for which the medicament was manufactured was novel and inventive, and not any further considerations under Article 52(4) EPC (cf. decision T 1020/03 *supra*, points (26) and (34) of the reasons).

4. Accordingly, the argument of Appellant II must fail. The requirements of Article 52(4) EPC are met.

Sufficiency of disclosure - Article 83 EPC

5. The medicament prepared according to claims 1 and 4 is used to kill tumor cells.

Appellant II argued that the medicament would show the desired effect only in cells having a mutation in a p53 gene, thus being deficient in p53 protein. The claims, not being restricted to these cells were however broader, with the consequence that they covered subject-matter which the patent did not disclose in a manner sufficiently clear and complete for it to be carried out by a skilled person, contrary to the requirements of Article 83 EPC.

6. The application as originally filed emphasises at different passages that the present invention is only concerned with the treatment of p53 associated cancers. In a specific chapter of the description on page 27, line 29 to page 29, line 23, which has the title "p53 and p53 mutations in cancer", it is said that "the p53 gene is a frequent target of mutational inactivation in a wide variety of human tumors and is already documented to be the most frequently-mutated gene in common human cancers." At the end of this chapter it is concluded that "it is thus possible that the treatment of p53 associated cancers with wild type p53 may reduce the number of malignant cells."

The Board judges that these passages in the description reflect the understanding of the reader that the claims only refer to embodiments relating to the killing of tumour cells susceptible to the indicated treatment.

Therefore, the Board judges that, contrary to Appellant's II argument, the patent in suit meets the requirements of Article 83 EPC.

Novelty - Article 54 EPC

7. Independent claims 1 and 4 define the chronological order of administration of the two pharmaceutically active entities. The tumor is first exposed to a DNA damaging compound (claim 1), respectively to DNA damaging radiation (claim 4), and then contacted with a p53 protein or gene.

Document (1), on page 693, left column, lines 13 to 16, reads as follows:

"Following 3-day direct intratumoral injection of Ad-p53, H358a tumors subcutaneously transplanted in nu/nu mice showed a modest slowing of growth; Ad-p53-injected tumors, however, regressed if CDDP was administered intraperitoneally for 3 days." (The abbreviation CDDP stands for cisdiamminodichloroplatinium also designated cisplatin).

8. The Board judges that this is not a disclosure of a mode of administration where the mice were first exposed to CDDP and then contacted with Ad-p53.

It is not justifiably to decide whether or not a document is prejudicial to novelty on the **basis of probability**. When a patent is revoked for lack of novelty the Board has to be **sure** that the facts disclosed in a prior art document anticipate the claimed subject-matter and that consequently the revocation is justified (cf. decision T 464/94 of 21 May 1997; point (16)).

- Consequently, the Board decides that the disclosure in document (1) does not anticipate the subject-matter of claims 1 to 5.
9. Documents (2) and (7) discuss the role of the p53 tumor suppressor for efficient activation of apoptosis triggered by ionizing radiation and several chemotherapeutic agents (document (2), page 957, summary, page 958, left column, page 963, left column, last paragraph; document (7), page 847, left column, end of first paragraph). They do not refer to the administration of a p53 protein or gene to a tumor cell.
10. Thus, claims 1 to 5 are novel over the teaching in the prior art documents on file and meet the requirements of Article 54 EPC.

Inventive step - Article 56 EPC

11. Document (1) is considered to represent the closest state of the art for the assessment of an inventive step (Article 56 EPC).

The subject-matter of claims 1 and 4 differs from the disclosure in document (1) in so far as the chronological order of the administration of the DNA damaging compound (agent) and the p53 protein or gene is defined.

12. According to Appellant I the problem underlying the present invention in the light of the disclosure in document (1) was the provision of an **improved method** to kill tumor cells.

Evidence for the achievement of an unexpectedly improved therapeutic effect, resulting from the timing of administration as disclosed in independent claims 1 and 4, namely first exposure to a DNA damaging compound or agent and then contact with a p53 protein or gene, could be found in document (14), (see page 1372, abstract; page 1373, left column, second full paragraph; Figure 2A; page 1377, right column, third full paragraph).

13. In the light of the disclosure in document (1), Appellant II defines the problem underlying the present invention as the provision of an **alternative method** to kill tumor cells. The solution to this problem, namely to choose a specific chronological order of administration of the two pharmacologically active entities, was considered to be obvious for a skilled person knowing the disclosure in document (1) and being taught in the application as filed that the target cells may be contacted "with the p53 protein or gene and the DNA damaging agent(s) or factor(s) at the same time" (page 7, lines 13 to 15 of the application as filed), or "... may be first exposed to the DNA damaging agent(s) and then contacted with a p53 protein or gene, or *vice versa*" (page 7, lines 24 to 26 of the application as filed), i.e. indicating that the order of administration was of no relevance.

14. Appellant II criticised that the application as filed did not contain any experimental data supporting the theory that the order of administration may have any influence on the efficiency of therapeutic method concerned. On the contrary, the skilled reader was told

that the order of administration was not critical and could be chosen freely (see point (12) above).

Document (14), which has been published more than two years after the claimed priority date, and which was the first disclosure going beyond speculation with regard to the influence of the sequential order of administration, should not be considered at all for the assessment of inventive step.

15. The Board agrees with both parties that the teaching of document (1) aims at the same objective as the claimed invention, namely killing of tumor cells, and requires the minimum of structural and functional modifications. According to established case law of the Boards of Appeal it thus represents the closest state of the art for assessing inventive step (Article 56 EPC).

The next step of the "problem and solution approach", consistently applied by the Boards of Appeal, is the definition of the problem underlying the invention claimed. The decisive question to be answered thereafter is, whether or not the cited prior art contains information that would encourage a skilled person, trying to solve this problem, to modify the disclosure in the closest prior art and to arrive at the claimed subject-matter in an obvious way.

16. The problem to be solved is defined differently by the parties. While Appellant I, by referring to the disclosure in post published document (14), defines the problem as the provision of an **improved method**, Appellant II takes the view the claimed invention serves to provide an **alternative** to the method

disclosed in document (1), (see points (12) and (13) above).

17. An effect which could be qualified to be unexpected can be regarded as an indication of inventive step if certain preconditions are met (cf. decision T 181/82; OJ EPO 1984, 401).

However, once a realistic technical problem has been defined and once it has been established that a particular solution to such problem would have been envisaged by a skilled person in the light of the relevant state of the art, that solution cannot be said to involve an inventive step, and this assessment is not altered by the fact that the claimed invention inherently also solves further technical problems (cf. decision T 936/96 of 11 June 1999). In the present case the surprising effect ("bonus effect") of an improved therapeutic activity resulting from the chronological order of administration as contained in the claims could not be regarded as an indication of the presence of an inventive step if this chronological order would be obvious.

On the other hand, should the Board decide that a skilled person trying to solve the problem as defined by Appellant II, namely the provision of an alternative method with regard to document (1), would not arrive at the subject-matter of claims 1 to 5 in an obvious way, there would be no need to further investigate the existence of a surprising effect substantiated in a post published document.

18. As already decided in point (8) above, document (1) does not disclose that the tumor cells are **first** exposed to a DNA damaging compound or agent and **then** contacted with a p53 protein or gene.

Appellant II has argued that the disclosure in document (1) came so close to the present invention that a skilled reader would not have needed any inventive skill to arrive at the claimed subject-matter.

When deciding whether or not the subject-matter of a patent claim is obvious in the light of a disclosure in a prior art document, the degree of similarity between the subject-matter of the claim and the teaching in the prior art document is not a decisive factor. Rather the question to be answered is, whether or not the cited prior art contains information that would encourage a skilled person, trying to solve this problem, to modify the disclosure in the closest prior art and to arrive at the claimed subject-matter in an obvious way.

The Board judges that document (1) itself does not contain any hint that would encourage the skilled reader to change its disclosure in a way to arrive at the subject-matter of claims 1 to 5. Appellant's II argument, for substantiating that claims 1 to 5 do not involve an inventive step in the light of the disclosure in document (1) alone, must fail.

19. Documents (2) and (7) report that the p53 tumor suppressor is required for efficient activation of the cell death program (apoptosis) triggered by ionizing radiation and several chemotherapeutic agents (document (2), page 957, summary, page 958, left column,

page 963, left column, last paragraph; document (7), page 847, left column, end of first paragraph). None of these two documents discloses the administration of a p53 protein or gene to a tumor cell, let alone the administration thereof after exposure of the cell to a DNA damaging compound or agent.

Moreover, the chronological order of administration as disclosed in independent claims 1 and 4 is not disclosed in any other of the prior art documents on file.

20. Consequently, the Board comes to the decision that a skilled person, trying to provide an alternative to the method disclosed in document (1) to kill tumor cells, would not arrive in an obvious way at the subject-matter of claims 1 to 5, either from the disclosure in document (1) taken alone or in combination with any other prior art document on file.

In the light of this decision the investigation of the existence of a surprising technical effect in the form of an improved therapeutic activity resulting from the specific chronological order of administration claimed, is not considered to be necessary (see point (17) above).

Claims 1 to 5 involve an inventive step and meet the requirements of Article 56 EPC.

Order

For these reasons it is decided:

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 with the claims and figures and a description to be adapted:

Claims: 1 to 5 according to the new main request
filed at oral proceedings;

Figures: Sheets 1/22 to 22/22 of the patent
specification.

Registrar:

Chair:

P. Cremona

M. Wieser