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D E C I S I O N
of 17 January 2001

Case Number: T 0800/99 - 3.3.4

Application Number: 95918867.3

Publication Number: 0758382

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Enhancing the sensitivity of tumor cells to therapies

Applicant:
Sidney Kimmel Cancer Center

Opponent:
-

Headword:
Cancer therapy/SIDNEY KIMMEL CANCER CENTER

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - main and auxiliary requests - no"

Decisions cited:
G 0005/83, T 0606/89

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0800/99 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 17 January 2001

Appellant: SIDNEY KIMMEL CANCER CENTER
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 10 March 1999 refusing European patent application No. 95 918 867.3 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

I. The appeal lies from the decision of the Examining Division dated 10 March 1999 to refuse the European application No. 95 918 867.3 with the international publication No. WO 95/30002 for lack of patentability of claim 1 under Article 52(4) EPC. The Examining Division also established that the claims then on file lacked novelty or inventive step.

Claim 1 refused by the Examining Division read as follows:

1. Method of increasing the effect of a cancer therapy comprising the steps of:

delivering wild-type therapy-sensitizing gene activity to a

tumor cell characterized by loss of said wild-type therapy-sensitizing gene activity, and

subjecting said tumor cells to said cancer therapy."

Independent claim 14 related to the same method wherein the specific wild-type p53 gene was delivered to, and expressed in, the tumor cells. Independent claim 24 related to the same method wherein the wild-type p53 protein was delivered to the tumor cell.

Dependent claims 2 to 13, 15 to 23 were directed to further features of the methods of claims 1 and 14, respectively.

Claims 25 to 27 related to the use of a therapy sensitizing gene, a cDNA encoding said therapy-sensitizing gene activity or a portion thereof for the

manufacture of a pharmaceutical composition to be used under specific conditions.

II. The Board sent a communication according to Article 11(2) of the rules of procedure of the Boards of appeal summoning oral proceedings and setting out its provisional non-binding opinion.

III. Oral proceedings took place on 17 January 2001. The Appellants (Applicants) filed one main request and two auxiliary requests in replacement of the claim request then on file.

Claim 1 of the main request read as follows:

"1. The use of a wild-type therapy-sensitizing p53 gene activity, a portion of said wild-type therapy-sensitizing p53 gene activity or a portion of a cDNA encoding said wild-type therapy-sensitizing p53 gene activity for the manufacture of a pharmaceutical composition for enhancing the ability of a cancer therapy to kill a tumor cell."

Claim 1 of auxiliary request I read as follows:

"1. The use of a wild-type therapy-sensitizing p53 gene activity, a portion of said wild-type therapy-sensitizing p53 gene activity or a portion of a cDNA encoding said wild-type therapy-sensitizing p53 gene activity for the manufacture of a pharmaceutical composition for enhancing the ability of a cancer therapy to kill a tumor cell, **wherein said tumor cell is a glioblastoma cell.**" (emphasis added by the Board).

Claim 1 of auxiliary request II read as follows:

"1. Method of enhancing the ability of a cancer therapy to kill a tumor cell, comprising the steps of :

delivering wild-type therapy-sensitizing p53 gene activity

to a tumor cell in-vitro wherein said tumor cell is characterized by loss of said wild-type therapy-sensitizing p53 gene activity, and

subjecting said tumor cells to said cancer therapy to kill said tumor cell."

IV. The following documents are cited in the present decision:

(3): Lowe, S.W. et al., Cell, Vol.74, pages 957 to 967, 1993,

(5): WO 94/06910

V. The arguments in writing and during oral proceedings by the Appellants are summarized as follows:

Main request

Article 54 EPC, novelty

- Document (5) taught that the introduction of the p53 gene in a heterogeneous population comprising hyperproliferative cells resulted in a suppression of the malignant phenotype of said cells. On the contrary, the subject-matter of claim 1 related to the use of the p53 gene activity in a medicament destined to kill tumor cells in order to enhance said killing effect. These two uses were opposite in their concept. Document (5) was not novelty destroying to the subject-matter of claim 1.

- Document (3) was not novelty destroying because it did not relate to the manufacture of a medicament.

Article 56 EPC, inventive step

- The closest prior art was document (3). This document taught that upon irradiation, $p53^{+/+}$ cells which had been made oncogenic by transfection with the E1A and T24 H-ras genes were more likely to die than the corresponding $p53^{-/-}$ cells. Yet, irradiation had very little effect on $p53^{+/+}$ cells coexpressing E1A and E1B. Because of these contradictory results, the teachings of document (3) were speculative.

- Furthermore, it was not clear that the experiments described in the "Results" section of document (3) had ever been carried out as no mention was made of either the ras gene or the E1B gene in the "Materials and Methods" section. If it was accepted on the sole basis of the "Results" section that the experiments had been carried out, then ambiguity remained as to the validity of the results obtained because it had not been controlled whether or not the part of the ras plasmid other than ras played a role in the effects observed. And, besides, it was left undefined whether the cells co-expressing E1A and T24 H-ras had been transfected by a plasmid carrying both genes or by two different plasmids. The skilled person would have understood the teachings of document (3) to be either erroneous or incomplete and thus, this document did not affect inventive step.

- Document (3) disclosed a phenomenon which only occurred in the very specific circumstance where E1a, T24 H-ras and the p53 genes were expressed in the same cells. The effect observed was due to this combination of factors rather than to the expression of the p53 gene alone. And, therefore, the subject-matter of claim 1 which only related to the effect of the p53 gene activity was not obvious.

First auxiliary request

This request was limited to the use of the p53 gene activity as a medicament in a cancer therapy against glioblastoma cells which were differentiated cells. The reasoning presented in relation to the inventive step of claim 1 of the main request still applied, all the more so, because in contrast to glioblastoma cells, the cells used in document (3) were undifferentiated cells.

Second auxiliary request

- A basis for claim 1 of this request was to be found on page 22, lines 10 and 11 of the application as filed.

- Document (5) was not detrimental to the novelty of claim 1 for the same reasons as given in relation to claim 1 of the main request.

  The claim was also novel over the teachings of document (3) because the feature that the p53 gene should be delivered to the tumor cell was not a feature of the method described in said document.

- The closest prior art was document (5) which disclosed an in vitro method for the introduction of the p53 gene and its subsequent expression, in malignant cells. Document (5) disclosed that the effect of said method was to revert the malignant phenotype, thus, it did not suggest that the introduction of p53 into malignant cells **concomitantly to cancer therapy** would lead to their death. Accordingly, the subject-matter of claim 1 was inventive.

VI. The Appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request, auxiliary request I, or auxiliary request II, all submitted at the oral proceedings on 17 January 2001.

Reasons for the Decision

Main request
Article 52(4) EPC

1. One of the reasons which led the Examining Division to refuse the application was that claims 1, 14 and 24 then on file comprised in vivo methods for increasing the effect of a cancer therapy ie. methods of treatment of the human body which were not patentable pursuant to Article 52(4) EPC.

2. Former claims 1 and 24 have been deleted from the main request presently on file. Claim 1 corresponding to former claim 14 is drafted as a claim to the use of the therapy-sensitizing p53 gene activity for the

manufacture of a pharmaceutical composition. All other claims (claims 2 to 10) are dependent on claim 1. Thus, the objection under Article 52(4) EPC does not apply any more. The invention is of the kind for which a patent may be granted providing the other requirements for patentability are fulfilled.

Article 54 EPC, novelty

3. Document (5) discloses the use of the p53 gene activity **to restore the normality of hyperproliferative cells** that contaminate preparations of autologous hematopoietic cells used for bone marrow reconstitution (page 8, lines 22 to 27). On page 13, lines 25 to 27, it is envisaged that the p53 gene can be added to a pharmaceutically acceptable carrier and administered to the patients ie that it is used in a pharmaceutical preparation.

4. Claim 1 relates to the use of the p53 gene activity for making a pharmaceutical preparation to be used as an enhancing factor in the **killing of hyperproliferative cells**, a different pharmaceutical use from that described in document(s).

5. Following the Enlarged Board decision G 5/83 (OJ 1985, 064, point 21), the novelty of a medicament may be derived from the new pharmaceutical use which is intended. Accordingly, as the pharmaceutical use for the pharmaceutical composition to which claim 1 is directed is not disclosed in document(s) the claimed subject-matter is novel over the teachings of document (5).

6. There are no other documents on file relating to the

use of the p53 gene activity for the manufacturing of a pharmaceutical composition. The requirements of Article 54 EPC are fulfilled.

Article 56 EPC, inventive step

7. The closest prior art is document (3). Said document describes a study of the effect of p53 gene expression on the mortality rate of oncogenically transformed embryonic fibroblasts when exposed to anti-cancer agents (ionizing radiation, chemical products). It is shown that $p53^{+/+}$ cells transfected with the E1A and T24 H-ras oncogenes experience significant death at low levels of ionizing radiations (1 Gy) whereas the corresponding $p53^{-/-}$ cells display no significant loss of growth when exposed to higher doses (5 Gy). The authors conclude on page 964: " ...the involvement of p53 in oncogene associated apoptosis represents a direct mechanism whereby p53 eliminates abnormally growing cells" and also: "...p53 status in tumor cells may be a strong determinant of response to treatment with either chemotherapy or radiation".

8. Starting from the closest prior art, the problem to be solved can be defined as putting into practice the knowledge that anti-cancer agents are more efficient at killing some oncogenically transformed cells when these express the p53 gene.

9. The solution provided is to prepare a pharmaceutical preparation containing p53 gene activity to be used in a cancer treatment.

10. Prima facie, this solution is a straightforward application of the teachings of document (3) that at

least the category of oncogenic cells which express E1a and T24 H-ras will be more responsive to cancer therapy when the p53 gene is expressed.

11. The Appellants challenged the validity of the experiments presented in document (3). They expressed doubts whether the transfection of the embryonic fibroblasts had ever been carried out or had been properly carried out (see section V above). In the absence of any factual evidence that these doubts are legitimate, the Board is not convinced by the arguments presented.

12. It was also argued that the skilled person would consider the results obtained in E1A, T24 H-ras $p53^{+/+}$ oncogenic cells as speculative because E1A, E1B $p53^{+/+}$ oncogenic cells remained resistant to radiation. However, this latter result is explained in document (3) by the already known fact that E1B counteracts the effect of p53 (page 959, left hand column). Thus, contrary to what is argued by the Appellants, the results obtained when E1A and E1B are expressed in the same cells are not inconsistent with p53 having a role in cellular death. In addition, the resistance to radiation being a property specific to E1B, it is in no way informative with regard to the results to be expected in E1A, T24 H-ras cells. Thus, the skilled person would have no reason to consider speculative the results obtained with these latter cells.

13. The Board's attention was drawn to the fact that the experiments in document (3) were carried out in oncogenically transformed cells rather than in tumor cells. The Board agrees to this remark, yet cannot see its relevance to inventive step since it is stated in

document (3), page 959 that "...oncogenically transformed fibroblasts provide an experimental system analogous to naturally occurring tumors...".

14. Despite the Appellants' arguments presented in points 11 to 13 above, the Board is convinced that the teachings of document (3) make it obvious to try and improve a cancer therapy against at least some naturally occurring tumors by using a pharmaceutical preparation comprising the p53 gene activity, while carrying out said cancer therapy, with a reasonable expectation of success. As claim 1 covers the use of the p53 gene activity for the manufacture of a pharmaceutical preparation for enhancing the therapy against any cancer cells, it comprises non inventive subject-matter. Therefore, the main request is refused for lack of inventive step.

First auxiliary request

15. Claim 1 is directed towards the same use for the p53 gene activity as was claimed in claim 1 of the main request **when the tumor cells are glioblastoma cells.** A basis for this claim is found on page 32 of the application as filed (Article 123(2) EPC).

16. The reasoning which led the Board to acknowledge novelty of the claim 1 of the main request (points 5 and 6, above) applies here as well.

17. The closest prior art is document (3). The problem to be solved can be defined as enhancing the effects of a cancer therapy against glioblastoma cells. The solution proposed is to make a pharmaceutical preparation containing the p53 gene activity to be used as

enhancer.

18. There is no evidence on file that the tumorigenic state of glioblastoma cells could not be due to the combination of E1A and T24 H-ras. When asked whether the skilled person would dismiss this possibility, the Appellants answered in the negative. Thus, it must be assumed that a category of cells falling under the denomination "glioblastoma cells" would be expected to be sensitive to radiation in the presence of the p53 gene activity. Accordingly, it is not inventive to use the p53 gene activity together with a cancer treatment to kill said category of cells. The reasoning developed in points 11 to 13 above in relation to the Appellants' arguments still applies.

19. Auxiliary request 1 is refused for lack of inventive step.

Auxiliary request 2

20. Claim 1 is directed to a method of enhancing the ability of a cancer therapy to kill a tumor cell in vitro. A basis for this method can be found on page 22, line 11 of the application as filed (Article 123(2) EPC).

21. Claim 1 is novel over the teachings of document (5) for the reasons given in relation to claim 1 of the main request (points 5 and 6, above). It is also novel over the teachings of document (3) because in this document, the p53 gene activity is the result of the expression of the p53 gene as a part of the oncogenic cells genetic information whereas, according to claim 1, the p53 gene activity is introduced into the cancer cells.

22. The Appellants argue that document (5) is the closest prior art. Document (5) describes an in vivo method of cancer treatment comprising an in vitro step whereby the hyperproliferative cells lacking p53 gene activity are made to express this activity by being transfected with the p53 gene, before they are reinjected into the cancer patients and the cancer treatment is carried out in vivo (page 8, lines 22 to 27).

23. Document (3) discloses a method to test the effect of the p53 gene activity on the resistance to cancer treatment of E1A, T24 H-ras oncogenically transformed cells in an vitro culture.

24. In accordance with the established case law of the Boards of appeal (cf. T 606/89 of 18 September 1990), the closest prior art for the purpose of assessing inventive step is that which corresponds to a similar use and requires the minimum of structural and functional modification. Thus, in the Board's judgment, document (3) is the closest prior art to the subject-matter of claim 1.

25. Starting from the closest prior art, the problem to be solved can be defined as providing an in vitro method for testing the efficacy of the p53 gene activity **in a cancer therapy against tumor cells which have lost this activity.**

26. The solution is to deliver the p53 gene activity to these cells in vitro and test their resistance to cancer agents.

27. This solution is directly derivable from the method of document (3) as it differs therefrom only by the fact

that the p53 gene activity is delivered to the tumor cells whereas in document (3), the oncogenic cells express the p53 gene as a function of their genetic patrimony. As these latter cells are said on page 959 "to provide an experimental system analogous to occurring tumors", the claimed method is neither surprising nor unexpected.

28. Auxiliary request II is, thus, refused for lack of inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

U. Bultmann U. Kinkeldey