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D E C I S I O N
of 27 April 2004

Case Number: T 1133/00 - 3.3.4

Application Number: 91307791.3

Publication Number: 0475623

IPC: A61K 48/00

Language of the proceedings: EN

Title of invention:
Genetic mechanisms of tumor supression

Patentee:
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

Opponents:
THE JOHNS HOPKINS UNIVERSITY
INTROGEN THERAPEUTICS, INC.
AVENTIS PHARMA S.A.

Headword:
Tumor suppression/UNIVERSITY OF CALIFORNIA

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

Keyword:
"Added subject-matter - main request and auxiliary request I - (yes)"
"Inventive step - auxiliary requests II, III, IV and V - (no)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1133/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 27 April 2004

Appellant I: (Opponent 2)
INTROGEN THERAPEUTICS, INC.
301 Congress Avenue, Suite 1850
Austin
Texas 78701 (US)

Representative:
Dehmel, Albrecht, Dr.
Dehmel & Bettenhausen
Patentanwälte
Herzogspitalstrasse 11
D-80331 München (DE)

Appellant II: (Opponent 3)
AVENTIS PHARMA S.A.
20, avenue Raymond Aron
F-92160 Antony (FR)

Representative:
Wachenfeld, Joachim, Dr.
Vossius & Partner
Postfach 86 07 67
D-81634 München (DE)

Respondent: (Proprietor of the patent)
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
300 Lakeside Drive
22nd Floor
Oakland
California 94612-3550 (US)

Representative:
Voelker, Ingeborg Carla Emmy
Uexküll & Stolberg
Patentanwälte
Beselerstrasse 4
D-22607 Hamburg (DE)

Party as of right:
(Opponent 1)

THE JOHNS HOPKINS UNIVERSITY
720 Rutland Avenue
Baltimore
Maryland 21205 (US)

Representative:

Bannerman, David Gardner
Withers & Rogers
Goldings House
2 Hays Lane
London SE1 2HW (GB)

Decision under appeal:

Interlocutory decision of the Opposition Division of the European Patent Office posted 18 September 2000 concerning maintenance of European patent No. 0475623 in amended form.

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: A. L. L. Marie
R. Moufang

Summary of Facts and Submissions

I. European patent EP 0 475 623 with the title "Genetic mechanisms of tumor suppression" was granted on the basis of five claims.

II. Opponents 1 to 3 filed oppositions and the revocation of the patent in suit was requested on the grounds that the requirements of Articles 100(a)(b)(c) EPC were not fulfilled, because of lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC), insufficiency of disclosure (Article 83 EPC) and extension of the subject-matter of the patent in suit beyond the content of the application as filed (Article 123(2) EPC).

III. In their interlocutory decision pursuant to Article 102(3) EPC the opposition division came to the conclusion that an amended set of five claims met the requirements of the EPC. Claim 1 read:

"1. Use of the wild-type p53 gene comprising the sequence of Table 3 for the preparation of a medicament for the treatment of cancer tumors, the cells of which having no endogenous wild-type p53 protein and being tumorigenic in nude mice, by suppression of the neoplastic phenotype, specifically including the tumorigenicity, of the cancer tumor cells."

IV. Notices of appeal against the decision of the opposition division were filed by Appellant I (opponent 2) and Appellant II (opponent 3) and their statements of grounds of appeal were replied to by the respondent (the patentee).

V. With his letter of 26 March 2004 the respondent filed auxiliary requests I to V and IIa to Va. Claim 1 of auxiliary requests I to V read:

Auxiliary request I:

"1. Use of the wild-type p53 gene comprising the sequence of Table 3 for the preparation of a medicament for the treatment of cancer, the cells of which having no endogenous wild-type p53 protein and being tumorigenic in nude mice, by suppression of the neoplastic phenotype, including the tumorigenicity, of the cancer cells."

Auxiliary request II:

"1. Use of the wild-type p53 gene comprising the sequence of Table 3 for the preparation of a medicament for the treatment of cancer tumors, the cells of which having no endogenous wild-type p53 protein and being tumorigenic in nude mice and capable of forming colonies in soft agar, by suppression of the neoplastic phenotype of the cancer tumor cells, wherein the suppression of the neoplastic phenotype of the cells includes the suppression of tumorigenicity as can be assayed in nude mice and includes the suppression of the neoplastic phenotype as can be shown by suppression of soft agar colony formation."

Auxiliary request III:

"1. Use of the wild-type p53 gene comprising the sequence of Table 3 for the preparation of a medicament for the treatment of cancer tumors, the cells of which having no endogenous wild-type p53 protein and being tumorigenic in nude mice and capable of forming colonies in soft agar, by suppression of the neoplastic phenotype of the cancer tumor cells, wherein the suppression of the neoplastic phenotype of the cells includes the suppression of tumorigenicity as can be assayed in nude mice and includes the suppression of the neoplastic phenotype of the cells as can be shown by suppression of soft agar colony formation and by difference in morphology, saturation density and growth rate of the cells as compared to cells having no endogenous wild-type p53 protein."

Auxiliary request IV:

"1. Use of the wild-type p53 gene comprising the sequence of Table 3 for the preparation of a medicament for the treatment of cancer tumors, the cells of which having no endogenous wild-type p53 protein and being human osteosarcoma cells, lung carcinoma cells, lymphoma cells or leukemia cells, by suppression of the neoplastic phenotype of the cancer tumor cells, wherein the suppression of the neoplastic phenotype of the cells includes the suppression of tumorigenicity as can be assayed in nude mice and includes the suppression of the neoplastic phenotype as can be shown by suppression of soft agar colony formation."

Auxiliary request V:

"1. Use of the wild-type p53 gene comprising the sequence of Table 3 for the preparation of a medicament for the treatment of cancer tumors, the cells of which having no endogenous wild-type p53 protein and being human osteosarcoma cells, lung carcinoma cells, lymphoma cells or leukemia cells, by suppression of the neoplastic phenotype of the cancer tumor cells, wherein the suppression of the neoplastic phenotype of the cells includes the suppression of tumorigenicity as can be assayed in nude mice and includes the suppression of the neoplastic phenotype of the cells as can be shown by suppression of soft agar colony formation and by difference in morphology, saturation density and growth rate of the cells as compared to cells having no endogenous wild-type p53 protein."

VI. Oral proceedings were held on 27 April 2004 in the presence of appellants I and II and of the respondent. The party as of right (opponent 1) had indicated in the letter of 23 April 2004 the intention not to attend the oral proceedings. During oral proceedings the respondent withdrew auxiliary requests IIa to Va.

VII. The appellants (opponents) requested that the decision under appeal be set aside and that the European patent No. 0 475 623 be revoked.

The respondent (patentee) requested that the appeals be dismissed (main request) or that the decision under appeal be set aside and the patent be maintained on the

basis of one of the auxiliary requests I, II, III, IV and V, all filed with letter of 26 March 2004.

VIII. The following documents will be referred to in the present decision:

(5) WO 90/05180

(6) D. Eliyahu et al., Proceedings of National Academy of Sciences USA, 1989, Vol. 86, pages 8763 to 8767

(7) C.A. Finlay et al., Cell, 1989, Vol. 57, pages 1083 to 1093

(26) H.-J. S. Huang et al., Science, 1988, Vol. 242, pages 1563 to 1566

(41) P. Recer, Level 1-7 of 14 Stories, The Associated Press, 23 August 1990

(42) R. Kolberg, Level 1-8 of 14 Stories, U.P.I., 23 August 1990

(43) R. Kolberg, Level 1-9 of 14 Stories, U.P.I., 23 August 1990

(44) Level 1-10 of 14 Stories, The Xinhua General Overseas News Service, 23 August 1990

(46) B. Alberts et al. in "Molecular Biology of the Cell", third edition, 1994, page 1256

(47) D.P. Lane and S. Benchimol, Genes & Development, 1990, Vol. 4, pages 1 to 8

(48) B.E. Weissman et al., Science, 1987, Vol. 236, pages 175 to 180

(51) Expert opinion of Dr. Curtis Harris

IX. The arguments submitted by appellants I and II in writing and during oral proceedings as far as they are relevant for this decision can be summarized as follows:

Main request and auxiliary requests II to V
Rule 57a EPC

The amendment in Claim 1 from "cancer" to "cancer tumors" was only allowable under Rule 57a EPC if one were prepared to accept that these terms were technically different. Since, however, the respondent argued under Article 123(2)(3) EPC that this amendment did not contravene these requirements of the EPC because there was no technical difference necessarily the amendment could not have been caused by an objection raised by the appellants or the decision under appeal and were thus not allowable under Rule 57a EPC. The same was true for the expression "specifically including the tumorigenicity".

All requests
Articles 83, 84, 123(3) and Rule 88 EPC

All claims 1 of all requests were not allowable under at least one of these Articles and the correction of the nucleotide sequence in Table 3 of the application as filed was not of the kind falling under the provision of Rule 88 EPC.

Article 123(2) EPC

The application as filed referred to five criteria which had to be considered together to determine the neoplastic phenotype of the cancer cells and did not indicate any difference in the suitability of these criteria for this purpose. The mention of the sole tumorigenicity in mice (claim 1 of the main request and of auxiliary request I) or of the combination tumorigenicity and soft-agar colony formation (claim 1 of auxiliary requests II and IV) amounted to an arbitrary selection and, hence, contravened the requirements of Article 123(2) EPC.

In documents (26) and (48) growth and tumorigenicity in nude mice were shown to be unrelated criteria for determining the neoplastic phenotype. However, no teaching on such an unrelatedness between growth and the ability to form soft-agar colony formation was to be retrieved from the prior art. In the patent in suit, this was shown only for the Saos-2 cells and further extended to other osteosarcomas. The subject-matter of claim 1 of auxiliary requests II and IV, which made reference to tumorigenicity and the ability to form colonies in soft agar to determine the suppression of the neoplastic phenotype, extended this teaching to all kinds of cancers, in which p53 gene was involved, and did not comply with the requirements of Article 123(2) EPC.

Article 56 EPC

The subject-matter of claim 1 of all requests did not involve an inventive step having regard to the teaching of documents (5), (26) and/or (47). In particular documents (5) and (26) disclosed in a very similar way the cure of retinoblastoma using the Rb gene as a tumor suppressor, in view of which the problem to be solved was to apply the use of the materials and methods described therein to other genes involved in cancers. An abundant prior art characterizing the p53 gene as a tumor suppressor led to the solution defined in the claims of the main and auxiliary requests in a "one way street"-manner.

X. The arguments submitted by the respondent in writing and during the oral proceedings as far as they are relevant for this decision were as follows:

Main request and auxiliary requests II to V
Rule 57a EPC

Both terms objected to by the appellants were introduced to meet either an objection of the opposition division in order to underline that the treatment of cancer took place *in vivo*, or of the appellants and were, thus, allowable under Rule 57a EPC.

All requests
Articles 83, 84, 123(3) and Rule 88 EPC

All arguments raised by the appellants under these provisions were answered.

Article 123(2) EPC

It was shown in the patent in suit (page 10, lines 39 to 51) and in the application as filed (page 21, line 6 to page 22, line 3) that the tumorigenicity in nude mice and the ability to form colonies in soft agar were two criteria sufficient for assessing the neoplastic phenotype of the cells. In particular, a separation between growth, on one side, and tumorigenicity and soft agar colony formation, on the other side, was indicated on page 10, lines 47 to 51 of the patent in suit (and corresponding page 21, lines 27 to 31 of the application as filed). This part of the description was the basis for the wording "*specifically including tumorigenicity*" and the limitation to either the tumorigenicity (claim 1 of the main request and auxiliary request I) or to its combination with the ability to form colonies in soft-agar (claim 1 of auxiliary requests II and IV) did not amount to added matter. Confirmation for this was found in document (26) and (48) in which growth and tumorigenicity were shown to be two separated features, since the cells carried on growing, although they no longer were tumorigenic in nude mice. This teaching was further not restricted to the Saos-2 cell line and the other osteosarcomas did not represent the maximum limit of its possible extension, since, although the patent in suit did make the proof of principle with the Saos-2 cell line, an osteosarcoma cell line, this principle was to be extended to all kinds of cancers involving p53 which were mentioned in the patent in suit on page 2, lines 23 to 25 and on page 6, lines 52 to 55

(page 2, line 31 to page 3, line 2 and page 13, lines 4 to 12 of the application).

Article 56 EPC

Documents (41) to (44), which were press releases issued one day before the priority date of the patent in suit, were the closest prior art. They taught that the insertion of the p53 gene into colon cancer laboratory cell lines prevented these cells from further growing. The problem to be solved in view of documents (41) to (44) was to find a method for treating colon cancer by inserting a normal gene and the solution defined in the claims of the main request and of auxiliary requests I to V was not obvious, because the suppression of cell growth evoked in documents (41) to (44) was not to be equated to the suppression of the neoplastic phenotype, as shown in documents (5), (26), (48) or in Exhibit 1 of document (51). Furthermore, these documents were not peer-reviewed and there was no technical indication on the methods and materials used (for instance, the colon cancer cells) or on the degree of inhibition of growth obtained. These experiments had only been carried out *in vitro* and no indication was given on whether they were representative for an *in vivo* process. Moreover, their authors were very cautious in their statements and drew attention (document (41)) to the fact that the delivery of the gene was a fundamental problem (which was not addressed to in these press releases) or that these results were no proof that colon cancer could be treated by inserting a normal gene into a patient. The conclusion of document (41) was that there was no obvious immediate clinical use of this teaching and

that this treatment of colon cancer may never be possible. It was further shown in document (42) that the addition of the mutated p53 gene to the colon cancer cells, the growth of which had been stopped by the wild-type p53 gene, restored the ability to grow, so that the problem was not solved, but still subsisted. On the contrary, it was shown in Table 2 of the patent in suit that the simultaneous introduction of mutant and wild-type p53 gene did not result in the growth of the Saos-2 cells studied. This result was unexpected in view of the widely accepted idea in the art of the dominant negative effect of the (product of the) mutated p53 gene scavenging the (product of the) wild-type gene. Furthermore, Exhibit 6 of document (51) showed that the system disclosed in the patent in suit was efficient in the treatment of cancers in humans.

If document (47) was considered as the closest prior art, the solution defined in the claims of the main and auxiliary requests I to V involved an inventive step, because document (47) was replete with unanswered questions, speculations and uncertainties. In particular, the dominant negative effect and the fact that adult cancers were multigenic cancers which could have required the blocking of the action of several genes involved in the cancer process, would have made the skilled person feel unconfident about the expectation of success in using the system developed in documents (5) or (26) for retinoblastoma, which was a monogenic cancer. Furthermore, document (47) showed that the p53 and Rb genes, apart from some similarities, also presented several differences.

The same consideration also applied when document (5) was considered as the closest prior art, because, also in this case, the dominant negative effect and the multigenic nature of adult cancers were not addressed.

The skilled person would have had no expectation of success, also because the technical field, from which the patent derived, was quite unexplored at the priority date and, furthermore, none of the documents cited above addressed tumorigenicity, but only growth, which was shown in documents (26) and (42) to be a phenomenon separated from tumorigenicity.

Reasons for the decision

All requests
Rules 57a, 88 EPC and Articles 83, 84, 123(3) EPC

1. A number of objections under the above provisions of the EPC have been raised by the appellants in view of amendments in claims 1 of all requests and in Table 3 of the specification. The board is not convinced by these objections but sees no need to give detailed reasons for its position since, as set out below (points 2 to 20), the patent must be revoked for other reasons.

All requests
Article 123(2) EPC

2. The mention in claim 1 of the main request and of auxiliary request I of the sole suppression of the tumorigenicity in nude mice for determining the

suppression of the neoplastic phenotype results, according to the appellants, in a selection of only one out of five features which was not as such disclosed in the application as filed and thus contravened the requirements of Article 123(2) EPC.

In the application as filed (page 18, lines 23 to 30) five criteria, namely morphology, growth rate, saturation density, soft agar colony formation and tumorigenicity in nude mice are indicated in relation to the assessment of the neoplastic phenotype (or its suppression). Of these five criteria two are applied in Tables 1 and 2 of the application as filed, namely soft-agar colony formation and tumorigenicity in nude mice, respectively, and the three others (morphology, growth rate and saturation density) in Figures 5, 6A and 6B and on page 21, lines 6 to 31 without any hierarchy or preference among these five criteria being indicated. There is no indication in the application as filed on whether each of these five criteria is *per se* sufficient for the assessment of the neoplastic phenotype. However, the sentence on page 21, lines 27 to 31 of the application as filed ("*The -50% reduction of growth rate of cultured Saos-2 cells by p53B was insufficient to account for the complete loss of tumorigenicity and soft-agar colony formation, implying that wild-type p53 specifically suppressed the neoplastic phenotype of these cells*") shows that suppression of the neoplastic phenotype has been observed and assessed using the loss of both the tumorigenicity and the soft-agar colony formation as criterion.

Therefore, there is a basis in the application as filed for the combined use of these two features as mentioned in the claims of auxiliary requests II to V. However, there is no basis in the above-mentioned disclosure or elsewhere in the application as filed for the sole use of tumorigenicity in nude mice as a criterion for the assessment of the neoplastic phenotype, as claimed in claims 1 of the main request and of auxiliary request I. It follows that the subject-matter of claim 1 of the main request and of auxiliary request I, referring to the sole tumorigenicity as criterion for assessing the neoplastic phenotype does not meet the requirements of Article 123(2) EPC, whereas that of claim 1 of auxiliary requests II to V, referring to both tumorigenicity and soft-agar colony formation, does.

3. The appellants objected to the generalisation of the results obtained with Saos-2 cells on the relationship between growth, tumorigenicity and soft-agar colony formation to all kinds of p53-related tumors, as done in claim 1 of auxiliary requests II to V, which was according to them not disclosed in the application as filed.

In the application as filed the results obtained with Saos-2 cells are first generalised to osteosarcomas with mutated p53 gene (page 21, line 4 to page 22, line 3). The patent in suit in the corresponding part of the description (page 10, lines 39 to 51) has the same formulation as the application as filed.

As far as the further generalisation of these results to p53-related tumors is concerned, it transpires from the whole application as filed that the determining element is the oncogenic/anti-oncogenic character of p53 gene. There is no evidence on file that other features of the tumor cell may modify the expression of this character. The Board considers it plausible that the results observed may be obtained with any tumor cell, the tumorigenicity of which is related to p53 gene. Therefore, the subject-matter of claim 1 of auxiliary requests II to V can be found in the application as filed.

It follows from the foregoing that the main request and auxiliary request I have to be rejected because the respective claims 1 do not fulfil the requirements of Article 123(2) EPC.

Auxiliary request II
Article 56 EPC

4. The subject-matter of claim 1 is basically directed to the use of the wild-type p53 gene comprising a particular DNA sequence for the preparation of a medicament for the treatment of cancer tumors.

5. The appellants have considered documents (5) or (47) as the closest prior art whereas the respondent has based the problem solution approach also on documents (41) to (44) as the closest prior art.

6. Document (47) is a review article which characterises the p53 gene as a suppressor gene, the inactivation of which is a prerequisite for the development of

malignancy, and stresses its similarities with the Rb gene. It summarizes the knowledge of the skilled person at its date of publication (the same year as the priority date of the patent in suit, i.e. 1990), and envisages further developments in this field. According to this document the p53 gene "seems to act as" a potent anti-oncogene in its wild-type form (page 5, left column, first paragraph, last sentence) and as an oncogene in its mutated form; this dual property was said to be the reason of the misinterpretation of its role arising from earlier experiments (page 2, left column, first paragraph and page 4, right column, second paragraph, first sentence). The presence of mutated p53 in several cancers is indicated (page 3, bridging paragraph between the right and left columns, and right column, last sentence) and is even defined as a prerequisite for the development of malignancy (page 4, right column, second paragraph, first sentence). The mode of action of the product of the p53 gene is also described in document (47) on page 4 (heading "*The normal function of p53*"): it acts by regulating the normal cell cycle. Similarities with the Rb gene are also mentioned in the paragraph bridging pages 5 and 6.

7. Documents (41) to (44) are press releases and hence are not peer-reviewed. They make the result of an investigation on the use of the p53 gene to prevent colon cancer cells from growing available to the public in general. They do not contain technical information on the way this result has been obtained. In particular, the colon cancer cells are not identified or characterized and the materials and methods used are not defined.

8. In view of the above analysis the board sees the teaching of document (47) as the closest one and the technical problem to be solved can be defined as the provision of a treatment for p53 related cancers.

9. The solution is defined in claim 1 of the main request (see section III above).

10. The question to be answered for the assessment of inventive step is whether this solution could have been deduced in an obvious manner from document (47) considered alone or in combination with other prior art documents mentioned above.

11. In order to support inventive step, the respondent argued that document (47) was replete with uncertainties and speculations. The board cannot see this in document (47) as far as the function and the mode of action of the wild-type p53 gene or its functional relationship to the Rb gene are concerned. It is an anti-oncogene working by regulating normal cell growth (page 4, headings "*The normal function of p53*" and "*p53 as an anti-oncogene*") and shares with the Rb gene many functional similarities, so that it is concluded on page 5 (heading "*Do p53 and Rb talk to each other?*") that both Rb and p53 proteins may be components of the same regulatory pathway and that a close functional connection exists between them. In view of this the next step to be carried out is formulated in document (47) on page 6 (left column, last three sentences of the first paragraph) as a question: "*Can wild-type p53 convert p53-deficient tumor cells back to normal growth behaviour as it*

appears Rb can for Rb-deficient cells?". This question thus summarizes the whole teaching of the prior art at the publication date of document (47), i.e. the technical standard reached in the prior art, and defines the next step to be taken by the skilled person. This question is followed in document (47) by a reference to a prior art document which is cited in the present appeal proceedings as document (26) and describes the suppression of the neoplastic phenotype in retinoblastoma cells by addition of the wild-type Rb gene. Document (26) thus provides the skilled person with the materials and methods to perform such tumor suppression. Therefore, it has to be concluded that the skilled person would obviously depart from document (47) and repeat the experiment disclosed in document (26), which led to suppression of retinoblastoma by the wild-type Rb gene, and would have had a reasonable expectation of success in arriving at the same point for the p53 gene.

12. The respondent denied that the skilled person would have had a reasonable expectation of success in doing so, because the teaching of document (26) concerned retinoblastoma, which is a children’s cancer involving only one gene, namely the Rb gene, and which could not be representative for multigenic adult cancers, i.e. cancers in which several genes were mutated. However, whether or not adult p53-related cancers are multigenic is irrelevant when considering inventive step of the subject-matter of claim 1 because of the mode of action of the p53 gene. Indeed, the anti-oncogenic action of the p53 gene was known to be due to the blocking of the normal cell cycle (document (47), page 5, heading "*The normal function of p53*"). From this knowledge the

skilled person would have concluded that the product of the p53 gene does not directly interact with all the genes which have possibly been mutated, but with the cellular machinery responsible for the growth, so that the number of the genes involved in malignancy is irrelevant for the performance of tumor suppression using the wild-type p53 gene.

13. The respondent based on the disclosure of document (48) an argument concerning the fact that the impact of the p53 gene has always been considered in the prior art by reference to the growth of the cells and not to their tumorigenicity, for which the growth cannot be representative. This document concerns the suppression of the neoplastic phenotype in Wilms' tumor cell line by introduction of normal chromosome 11 which is shown on page 178 (right column, last sentence of the second paragraph) to have little effect on the growth behaviour of the cells in culture despite the definite effect upon their ability to form tumors in nude mice. It is concluded in document (48) (page 179, right column, second paragraph) that the Wilms' tumor suppressor gene seems to regulate a late stage in the progression to malignancy rather than one of the initial preneoplastic stages, a late stage which obviously lies after the "growth stage". However, since a cancer cell is defined on page 1256 of document (46), a textbook on the molecular biology of the cell and thus representing the common general knowledge of the skilled person, as being able to reproduce in defiance of the normal restraints and to invade or colonize territories normally reserved for other cells, the ability to grow is a necessary condition for a cell to be tumorigenic. This is in agreement with the teaching

of the patent in suit on page 10, lines 47 to 51, according to which "*the -50% reduction of the growth rate of the Saos-2 cells was insufficient to account for the loss of tumorigenicity*", since this sentence indicates nothing else than the link between growth and tumorigenicity. Growth is a necessary, but not a sufficient condition for tumorigenicity, ie there is no tumorigenicity in the absence of growth, but the presence of growth does not necessarily imply tumorigenicity. As shown in the case described in document (48), the suppressor gene interacts with a step of the tumorigenic pathway which lies after the growth step, so that the cell treated with the suppressor gene, although no longer being tumorigenic, can still grow. Therefore, the expectation of success of the skilled person would not have been hindered by the fact that the prior art documents do not deal with the tumorigenicity of the cells treated with p53, but only with the suppression of their growth, since in document (47), summarizing the teaching of these prior art documents, p53 was shown to block the growth of the cancer cells and, as a consequence, their tumorigenicity, since the former, as stated above, is a necessary condition for the latter.

14. The "dominant negative effect" argument submitted by the respondent to underline the position that the skilled person had no reasonable expectation of success seems to be based on the prior art explaining the interaction between the two alleles of the p53 gene during the progression of a cell to malignancy. In particular, it was assumed, as reported in document (47) (page 5, right column, heading "*Mutant p53 as dominant negative mutants-oncogene or anti-oncogene?*") that the

mutant p53, which has a much longer half-life than the wild-type form (page 3, right column, heading "*Properties of activated mutant p53s*"), could bind and neutralize the product of the wild-type p53 gene or compete with it for binding to its normal substrate. However, the board is also not convinced by this position because the wild-type p53 gene was shown to have an influence on the growth of cells despite the presence of the product of the mutant p53 gene, as shown in document (47) on page 4 (heading "*p53 as an anti-oncogene*") quoting a document cited in the present proceedings as document (7). In this document the addition of the wild-type p53 gene is shown to hinder the transformation of rat embryo fibroblasts by mutant p53 gene associated with *ras*, as seen by the inhibition of the induction of transformation foci. This teaching is confirmed by the disclosure of document (6) on page 8764 (left column, last paragraph) in which the wild-type p53 gene is said to inhibit focus induction even in presence of an excess of mutated p53.

15. Therefore, in view of the above, the Board is convinced that the skilled person was induced by the teaching of document (47) to take an ineluctable step, i.e. the application of the experiments done with retinoblastoma and Rb gene, as described in document (26), to p53-related cancers. The Board is further convinced that the skilled person would have had a reasonable expectation of success in doing so.

16. The same conclusion would have been reached if document (5), the disclosure of which is very similar to that of document (26), would have been considered as the closest prior art. The technical problem would then

have been to extend the teaching of this document to other cancer forms, in which an oncogene/anti-oncogene was involved. The cited prior art, for instance document (47), showed that p53 was the only tumor suppressor cloned at that time, so that the skilled person would obviously have chosen this track. As far as the expectation of success is concerned the same arguments, as developed above, apply here too.

17. Whether or not one might have arrived at the claimed subject matter in a non-obvious way when departing from either of documents (41) to (44), as argued by the respondent (see for details section X above), is irrelevant. It is the board's task to define the skilled person and to judge which route he would have taken. If it was obvious for the so defined skilled person to arrive at a claimed subject matter when following this route, arguing another possibly inventive route cannot save the case.

Auxiliary requests III to V
Article 56 EPC

18. All claims 1 of these requests refer, like claim 1 of auxiliary request II, to the use of the wild-type p53 gene for the preparation of a medicament for the treatment of cancer tumors, which the board decided above not to be inventive for auxiliary request II. Further features included in the respective claims 1 are:

Auxiliary request III: the ability of the cancer cells to form colonies in soft agar and the determination of the suppression of the neoplastic phenotype of the

cells as shown by suppression of this ability and differences in morphology, saturation density and growth rate.

Auxiliary request IV: the suppression of the neoplastic phenotype as shown by the same feature as in auxiliary request II and the tumor cells are specified as being human osteosarcoma cells, lung carcinoma cells, lymphoma cells or leukemia cells.

Auxiliary request V: the cells are specified as in auxiliary request IV and the suppression of the neoplastic phenotype is determined by the same features as in auxiliary request III.

19. The additional features mentioned above cannot, in the Board's opinion, contribute to the inventive step of claim 1 of auxiliary requests III to V, since the types of cancers mentioned were already known to be related to p53 (document (47), page 3, right column, last sentence) and the five criteria were well-known in the art for the assessment of the neoplastic phenotype, as shown in the abstract of document (26), for instance.

20. Therefore, the reasoning set out above in points 4 to 17 in view of inventive step for claim 1 of auxiliary request II applies for these claims as well and renders the subject matter of claims 1 of all these requests equally non-inventive so that the requirement of Article 56 EPC is not fulfilled.

21. Since all of the auxiliary requests II to V contain a claim which does not fulfil the requirement of Article 56 EPC they must be rejected.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey