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D E C I S I O N
of 2 June 2005

Case Number: T 0558/03 - 3.3.4

Application Number: 90301817.4

Publication Number: 0390323

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
Detection of loss of the wild-type p53 gene

Patentee:
THE JOHNS HOPKINS UNIVERSITY

Opponents:
01: INTROGEN THERAPEUTICS, INC.
02: Rhône-Poulenc Rorer

Headword:
Wild-type p53 gene/JOHNS HOPKINS UNIVERSITY

Relevant legal provisions:
EPC Art. 83, 114(2), 111(1)

Keyword:
"Late filed requests (no)"
"Sufficiency of disclosure, main request, auxiliary requests I-III (no), auxiliary request IV (yes)"
"Remittal to the first instance (yes)"

Decisions cited:
T 0292/85, T 0011/89, T 0689/90, T 0396/99

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0558/03 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 2 June 2005

Appellant: (Proprietor of the patent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 19 March 2003 revoking European patent No. 0390323 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairwoman: U. Kinkeldey
Members: M. Wieser
G. Weiss

Summary of Facts and Submissions

I. The appeal was lodged by the Patent Proprietors (Appellants) against the decision of the Opposition Division, whereby the European patent No. 0 390 323 was revoked according to Article 102(1) EPC.

II. The patent has been granted with claims 1 to 37. Claim 1 thereof read as follows:

"A method of diagnosing a neoplastic tissue of a human, comprising: detecting loss of wild-type p53 genes or their expression products in isolated human tissue suspected of being neoplastic, wherein said loss leads to non-functional p53 gene products, loss of expression of p53 mRNA or diminution of expression of p53 mRNA, said loss indicating neoplasia of the tissue."

III. The patent had been opposed by Opponents 01 and 02 (Respondents I and II) under Article 100(a) 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 (Article 83 EPC) and under Article 100(c) EPC on the ground of added subject-matter (Article 123(2) EPC).

IV. The Opposition Division had decided that claims 36 and 37 of the main request before them did not meet the requirements of Article 123(2) EPC, that claims 33 and 34 of the first auxiliary request were not allowable under Article 52(4) EPC and that claims 33 and 34 of the second auxiliary request did not meet the requirements of Article 123(3) EPC. Finally, they

decided that claim 1 of the third auxiliary request before them, which was identical to claim 1 as granted (see section (II) above), did not fulfil the requirements of Article 83 EPC.

V. With the grounds of appeal the Appellants requested maintenance of the patent on the basis of an amended main request.

The Board had issued a communication on 6 December 2004. In response, the Appellants on 1 April 2005 filed new auxiliary requests I to V. With a further submission, received by fax on 27 May 2005, the Appellants filed a new main request and auxiliary requests I to IV. The new main request and auxiliary request I differed from the previous requests (1 April 2005) in claim 35 only. The new auxiliary requests II to IV corresponded to previous auxiliary requests III to V.

Oral proceedings were held on 2 June 2005.

The Appellants (Patent Proprietors) requested that the decision under appeal be set aside and that the patent be maintained on the basis of:

claims 1 to 36 of the main request, or
claims 1 to 36 of the auxiliary request I, or
claims 1 to 34 of the auxiliary requests II, III or IV,

all filed by fax received on 27 May 2005.

The Respondents I and II (Opponents O1 and O2) requested that the appeal be dismissed.

VI. Claim 1 of Appellants' main request, auxiliary requests I and II were identical to claim 1 as granted (see section II above).

Claim 1 of auxiliary request III read as follows:

"A method of diagnosing a neoplastic tissue of a human, comprising: detecting loss of wild-type p53 genes or their expression products in isolated human tissue suspected of being neoplastic, **compared to normal tissue isolated from the human**, wherein said loss leads to non-functional p53 gene products, loss of expression of p53 mRNA or diminution of expression of p53 mRNA, said loss indicating neoplasia of the tissue." (Emphasis added by the Board).

Claims 23 of Appellants' main request and auxiliary requests I to III read as follows:

"A method of supplying human wild-type p53 gene function to a human cell which has lost said gene function by virtue of mutation in a p53 gene wherein said mutation leads to non-functional p53 gene products, loss of expression of p53 mRNA or diminution of expression of p53 mRNA wherein the presence of said mutant p53 gene or expression product indicates the presence of a neoplastic tissue in the human, comprising:

introducing in vitro a wild-type p53 gene into the cell such that said gene is expressed in the cell."

VII. Claim 1 of auxiliary request IV read as follows:

"A method of diagnosing a neoplastic tissue of a human, comprising: detecting loss of wild-type p53 genes or their expression products in isolated human tissue suspected of being neoplastic, wherein said loss leads to non-functional p53 gene products, loss of expression of p53 mRNA or diminution of expression of p53 mRNA, said loss indicating neoplasia of the tissue, **wherein the wild-type p53 gene sequence is shown in Zakut-Houri et al., EMBO J., 4, 1251-1255, 1985."** (Emphasis added by the Board).

The same definition of the wild-type p53 gene sequence was contained in claim 23 and in all other independent claims of this request (either explicitly or by back-reference to claim 1).

VIII. The present decision refers to the following documents:

(16) Mol.Cell.Biol., vol.6, 1986, pages 1379 to 1385

(21) EMBO J., vol.4, 1985, pages 1251 to 1256

(22) Mol.Cell.Biol., vol.6, 1986, pages 4650 to 4656

(23) Mol.Cell.Biol., vol.7, 1987, pages 961 to 963

(24) Gene, vol.70, 1988, pages 245 to 252

(25) PNAS, vol.92, 1995, pages 3963 to 3967

(50) Cancer Res., vol.52, 1992, pages 4335 to 4341

(51) Mol.Cell.Biol., vol.13, 1993, pages 3811 to 3820

(52) Nature, vol.342, 1989, pages 705 to 708.

IX. The submissions made by the Appellants as far as they are relevant for the present decision may be summarised as follows:

The claims of the newly filed requests did not contain extensive amendments when compared to the claims as granted and to the claims before the Opposition Division, They could not have taken the Respondents by surprise. They have been filed in response to the decision under appeal and to the arguments of the Respondents and helped to expedite the procedure. Therefore, they should be allowed into the proceedings.

The term "wild-type gene" was well known and commonly used in the here relevant technical field as including all polymorphisms and excluding all mutations of a known gene. The skilled reader at the day of filing of the patent in suit could have verified if a sequence was a p53 wild-type sequence or not by applying several tests disclosed in the description. The fact that one out of five reference sequences disclosed in the exemplary part of the patent later turned out to be a mutant sequence, did not lead to an insufficiency of disclosure, as the skilled person, upon application of said tests, immediately would have recognized that the sequence in question, which was derived from a cancer cell line, was not a wild-type sequence. Therefore, the main request and auxiliary requests I to III did not violate Article 83 EPC.

The claims of auxiliary request IV had a basis in the application as originally filed (Article 123(2) EPC) and were clear according to the requirements of Article 84 EPC. The term "wild-type p53 gene" was precisely defined in the independent claims. Thus, the invention, referring to methods, kits and nucleic acid probes, was disclosed in a manner sufficiently clear and complete for it to be carried out by a skilled person (Article 83 EPC).

X. The submissions made by Respondents I as far as they are relevant for the present decision may be summarised as follows:

All of Appellants' requests were submitted late and were filed without accompanying substantive explanations. They contained amendments not previously contained in the claims and took the Respondents by surprise. According to the case law of the Boards of Appeal these requests should be disregarded as foreseen in Article 114(2) EPC.

In order to carry out the claimed invention a skilled person at the date of filing of the patent in suit, must have known the sequence of the wild-type p53 gene. The patent itself did not contain a disclosure of this sequence, but referred to five prior art documents in examples 2 and 4, which allegedly disclosed p53 wild-type sequences. However, as one of these prior art sequences later turned out to be a tumorigenic mutation, the invention according to Appellants' main request and auxiliary requests I to III was not sufficiently disclosed and violated the requirements of Article 83 EPC. The skilled person, when practising the

claimed method and obtaining a result, which in the light of the disclosure of the patent had to be considered as being negative, had no reason to carry out tests to verify if the obtained result was correct or not.

Claim 1 of auxiliary request IV contravened the requirements of Articles 84 and 123(2) EPC.

XI. The submissions made by Respondents II as far as they are relevant for the present decision may be summarised as follows:

All of Appellants' requests were late filed and should be disregarded. Respondents' I arguments with regard to lack of sufficiency of disclosure of the main request and of auxiliary requests I to III were shared.

In addition, with regard to auxiliary request III, even when assuming that the formulation inserted into claim 1 of this request was able to overcome the objection under Article 83 EPC, it had to be noted that, among others, independent claim 23 did not contain this amendment.

Claim 1 of auxiliary request IV was not clear (Article 84 EPC) and extended the patent beyond the content of the application as filed (Article 123(2) EPC).

Reasons for the decision

Admissibility of Appellants' requests (Article 114(2) EPC)

1. To expedite the proceedings, parties are supposed to submit all facts, evidence and requests at the outset of appeal proceedings, or - if this is not possible - as soon as they can. The Board has to ensure that proceedings are conducted expeditiously, and the parties fairly treated, e.g. not taken by surprise by what is called a "new case" filed at a late phase of the proceedings (cf Case Law of the Boards of Appeal of the European Patent Office, Chapter VI.F, 4th edition, 2001).

2. The Board agrees with the Respondents that Appellants' final requests have been filed at a very late stage of the proceedings as they were received by fax on 27 May 2005, thus within one week before the oral proceedings held on 2 June 2005.

   However, as stated in sections (V) and (VI) above, claim 1 of Appellants' new main request and auxiliary requests I and II was identically contained in the main request before the Opposition Division (and is identical to claim 1 as granted). Claim 23 of the new main request and of auxiliary requests I to III was identically contained in the main request before the Opposition Division.

3. These are claims at issue (see reasons). Therefore, the Board, at its discretion under Article 114(1) EPC, and considering that the above stated facts do not result

in an unfair treatment of the Respondents, allows these requests into the procedure.

4. In claim 1 of auxiliary request IV, and in all other independent claim of this request, the sequence of the wild-type p53 gene has been characterised as being identical to the sequence disclosed in document (21).

This amendment has been carried out in reaction to the decision of the Opposition Division, which in point (7.3) of the decision under appeal found that a claim generally referring to a "wild-type p53 gene" violates the requirements of Article 83 EPC. After the Board, in point (8) of their communication of 6 December 2004, have signalized the parties that they tend to share the Opposition Division's point of view in this respect, the Appellants on 1 April 2005, thus within the time limit set by the Board for making written submissions, which was set at two months before the oral proceedings, filed a new auxiliary request V (which corresponds to the present auxiliary request IV).

The Board judges that the Appellants, by filing auxiliary request IV at a late stage of the procedure, have nonetheless not abused the procedure as they acted as soon as they became aware that the Board is of the preliminary opinion that the Opposition Division decided correctly.

Auxiliary request IV is therefore allowed into the proceedings.

Main Request

Sufficiency of disclosure (Article 83 EPC)

5. Claim 1 refers to a diagnostic method based on the analyses of the p53 gene sequence in the cells of a tissue sample and on the comparison of the detected sequence with wild type p53 genes.

Claim 23 relates to a method of supplying human wild-type p53 gene function to a human cell having lost said function, comprising introducing in vitro a wild-type p53 gene into the cell such that said gene is expressed in the cell.

The p53 gene codes for protein p53, which is described in the art as being a "tumour suppressor protein" (document (51), abstract). Loss of wild-type p53 genes or their expression products indicates neoplasia of a tissue.

In order to be able to evaluate the results of the methods of claims 1 and 23 the skilled practitioner **must** be in possession of the wild-type p53 gene sequence.

6. The patent does not explicitly disclose what a wild-type p53 gene is. Instead of this it refers on page 6 lines 16 to 20 (corresponding to column 10, line 55 to column 11, line 8 of the application as originally filed) to five prior art documents which allegedly disclose human wild type p53 genes. This passage reads:

"First, p53 cDNA probes detecting exons spread over 20,000base pairs (including all protein encoding exons) [P. Lamb, L.V.Crawford, Mol. Cell. Biol. 6, 1379 (1986); R. Zakut-Houri, B.Bienz-Tadmor, D. Givol, M. Oren, EMBO J. 4, 1251(1985); N. Harris E.Brill, O. Shahat, M. Prokocimer, T.E. Admas, Mol. Cell. Biol., 6, 4650(1986); G. Matlashewski et al., Molec. Cell. Biol. 7, 961 (1987); V.L.Buchman et al., Gene 70, 245 (1988)] were used to examine the DNA of 82 colorectal carcinomas (50 primary specimens and 32 cell lines)in Southern blotting experiments."

The reference to these five publications, documents (16), (21), (22), (23) and (24) in the present procedure, is repeated on page 7, lines 23 to 24 (column 13, lines 21 to 23 as filed).

7. Document (16) discloses in figure (2) on page 1381, the DNA sequence of the human p53 gene and the predicted amino acid sequence of the protein. Differences between this sequence and human p53 cDNA are indicated. The figure shows three sequences, a "main sequence", and two sequences containing changes in one single nucleotide. In the first case a change from CGC to CCC results in change at codon 72 from Arginine to Proline (R72P), in the second case a change from CGT to CAT at codon 273 results in a change from Arginine to Histidine (R273H). The "main sequence" is also disclosed in documents (22), (23) and (24). R72P is also disclosed in documents (21), (22), (23) and (24). Document (23) additionally refers to a sequence containing Cystein at position 72, document (22) discloses a sequence with Threonine instead of Alanine at position 79.

Thus, the five documents disclose five different sequences which all are disclosed to represent a human wild-type p53 sequence.

8. Document (52), published eight months after the claimed priority date and naming three of the present inventors as authors, discloses for the first time that one of the p53 sequences published in document (16), namely R273H, in fact is not a wild-type sequence but a tumorigenic mutation (see page 705, right column, third full paragraph). The same information is conveyed in document (25), published five years after the priority date (see table 1 on page 3965).

9. The consequences of this post-published disclosure are as follows:

The patent in suit does not disclose the decisive technical feature which is necessary for a skilled person to carry out the claimed invention, namely the correct sequence of human wild-type p53 genes.

A skilled reader practising the invention according to claim 1, after having sequenced the p53 gene contained in the cells of the sample, will compare the detected sequence with the five sequences disclosed in documents (16) and (21) to (24). If the sequence turns out to be identical to one of the five sequences which are defined in the patent as being wild-type p53 sequences, the result of the diagnostic test will be classified as negative, which means that the tissue sample does not contain neoplastic tissue. If, however, the detected sequence is identical to the R273H sequence disclosed

in document (16), which has turned out to be a tumorigenic mutation, this result would wrongly be classified as negative.

As a result neoplastic tissue of a human patient would be misjudged as being not neoplastic. Besides the fact that this shortcoming of the method according to claim 1 manifests a violation of the requirements of Article 83 EPC, it has the undesirable implication that a wrong negative result in terms of the diagnosis of tumours might have potentially disastrous effects for the human patient concerned.

When trying to supply human wild-type gene p53 function to a cell, according to claim 23, introduction of the R273H mutant into the cell will not result in a reactivation of the wild-type function.

10. The Appellants argue that a skilled person reading the patent in suit is provided with information encouraging him/her to test if the sequences disclosed in the cited prior art documents really are wild-type sequences. These tests allow him/her to find out that this is not the case for the R273H sequence disclosed in document (16).

According to the Appellants a first test is described in column 8, lines 24 to 52 of the application as filed, where it is said that the introduction and expression of a wild-type p53 gene in a cell carrying a mutant p53 allele results in non-neoplastic growth of the cell. Thus, by monitoring the desired effect, e.g. non-neoplastic growth of the cell, one can determine

whether the inserted gene was a wild-type p53 gene or not.

Another test, based on screening of loss of wild-type p53 protein function is said to be disclosed in column 6, lines 23 to 33 of the application as filed. Loss of ability of the p53 protein to bind to either of SV40 large T antigen or to the adenovirus E1B antigen indicates a mutational alteration of the protein which reflects a mutational alteration of the gene itself. Documents (50), published three years after the priority date (see page 4336, top of left column and first full paragraph, right column), and document (51), published four years after the priority date (see page 3817, right column, last paragraph) disclose that R273H does not bind to SV40 large T antigen.

Finally, the Appellants argue that example 5 (in columns 14 to 15 of the application as filed), discloses a test to ensure whether a sequence change represents a mutation rather than a polymorphism. This test comprises comparing the sequence containing the candidate mutation/ polymorphism obtained from a tumour of an individual with the p53 sequence obtained from normal cells of the same individual. If the sequence change is present in a normal cell it is a polymorphism, if not it is a mutation.

11. The Board does not agree that a lack of sufficient disclosure can be cured by a reference to these tests, which are not considered to put a skilled person into the position where he/she is able to carry out the invention as described in the specification and as defined in claims 1 and 23 without undue burden.

The specification, by reference to five prior art documents, discloses five sequences which are designated as wild type p53 gene sequences, and which a skilled person carrying out the methods claimed would use as reference sequences. At no point in the specification or in the claims, the skilled person is advised to carry out any of the tests identified in point (11) above to verify that the obtained results are correct. He/she would have no reason to carry out any further tests.

In case of the method of claim 1, the skilled person would not be aware that some of the negative results in fact were wrong negative results.

12. In addition, the tests specified by the Appellants and referred to in point (11) above partly are not considered to be conclusive, partly involve undue burden.

The introduction of a wild-type gene into a cell carrying a mutant allele, wherein the wild type gene either remains extrachromosomal or recombines with the endogenous mutant gene, as described in column 8 of the original application, is a laborious and time consuming undertaking. The observation whether or not in the present case the inserted gene is a wild-type gene depends on a number of circumstances. This is evident from the cautious language used in the relevant passage of the specification in column 8 (*"..the wild-type p53 gene or gene portion **should** be expressed to a higher level than that of the mutant gene", or "...such recombination **would** require a double recombination*

*event which **would** result in the correction of the p53 gene mutation."* emphasis added by the Board).

The loss of ability of R273H to bind to the SV40 large T antigen is described in post published document (52) only in case of the entire protein. In contrast, fragments of this mutant protein expressed as fusion proteins in E.coli were found to bind the antigen (see document (52), table 1 and page 3817, right column, last paragraph).

Finally, the passage in example 5 of the patent, which the Appellants consider to disclose a generally applicable test for determining whether a sequence change represents a mutation rather than a sequence polymorphism, specifically refers to the assessment of a sequence change at codon 175 of the p53 gene. Moreover, a method relying on the comparison of the p53 gene in normal and tumorigenic tissue of the **same** individual, seems to be of little use, at least in a diagnostic or therapeutic context.

13. Following another line of argumentation, the Appellants by referring to decision T 292/85 (OJ EPO 1989, 275), argue that it is irrelevant that one of the sequences disclosed in document (16), namely R273H, cannot be used in the claimed methods as long as there are four other suitable sequences disclosed which represent the human wild-type p53 sequence.

The Board does not consider decision T 292/85 to be applicable in the present case as it is related to a different technical situation. Contrary to the present case, where one embodiment of the invention which is

explicitly disclosed in the description, is not suitable to perform the invention, the Board, in decision T 292/85 held that the non-availability of some particular variants was immaterial as long as there were suitable variants which provided the same effect.

14. The patent in suit does not contain a reliable definition of the wild-type p53 gene, which would allow a skilled person to identify it. In fact one out of five sequences, disclosed in the patent by reference to prior art documents as being wild type sequences, later turned out to be a tumorigenic mutant.

Therefore, neither a diagnostic method comprising the detection of loss of wild-type p53 genes, according to claim 1, nor a method of supplying human wild-type p53 gene function to a cell which has lost said function, according to claim 23, are disclosed in the patent in a manner sufficiently clear and complete for it to be carried out by a skilled person.

The requirements of Article 83 EPC are not met.

Auxiliary Requests I and II

15. Claims 1 and 23 of these requests are identical to claim 1 of the main request. The decision taken with regard to the main request applies equally to auxiliary requests I and II.

Auxiliary Request III

16. Claim 1 of auxiliary request III is distinguished from claim 1 of the previous requests by insertion of the term *"compared to normal tissue isolated of the human"* (see section (VI) above).

A decision as to whether claim 1 of auxiliary request III meets the requirements of Article 83 EPC is not considered to be necessary in the present case. As claim 23 of this request is identical to claim 23 of the main request, the requirements of Article 83 EPC are not met for this reason alone.

Auxiliary Request IV

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

17. In claim 1 of auxiliary request IV, and in all other independent claims of this request (either explicitly or by back-reference to claim 1), the wild-type p53 gene sequence is defined as being **"...shown in Zakut-Houri et al., EMBO J., 4, 1251-1255, 1985."**

This document, designated in the present procedure as document (21), discloses in figure 2 on page 1252 the nucleotide sequence and deduced amino acid sequence of the entire coding region of human p53 cDNA in comparison with mouse p53 cDNA. No other gene sequences are contained in the document. Document (21) is one out of the five documents which are cited in column 10, line 55 to column 11, line 8 and column 13, lines 21 to 23 of the originally filed application, as disclosing

human wild-type p53 gene sequences (see point (6) above).

Probes generated from a fragment of the cDNA clone disclosed in document (21) were used in examples 3 (see passage bridging columns 11 and 12) and in example 4 (see passage bridging columns 13 and 14 of the application as filed).

18. The Respondents argued that features which are not disclosed in the description of the invention as originally filed but which are only described in a cross-referenced document which is identified in such description are prima facie not within "the content of the application as filed" for the purpose of Article 123(2) EPC. It is only under particular conditions that such features can be introduced by way of amendment into the claims of an application, which conditions were not met by the patent in suit. They referred in this respect to decision T 689/90 (OJ EPO 1993, 616).

19. Claim 1 of the patent underlying decision T 689/90 included the feature that "at least one of the locating member (11) and the return member (12) comprises a metal core and an elongate jacket which electrically surrounds the core and which is composed of a conductive polymer", which was not contained in the application as filed. The description as originally filed included the following sentence in particular which was said by the Applicant to provide a proper basis for the above feature: "For further details of suitable locating, source, and return members, reference should be made to the application

corresponding to US Serial No. 509 897". The Board decided that features incorporated from the cited prior art document into claim 1 contravened Article 123(2) EPC (see point (4) of reasons for the decision).

The present situation, where the application as originally filed contains an explicit basis for the amendment, namely a statement that document (21) discloses a wild-type p53 sequence, is different. In contrast to the facts underlying decision T 689/90, where the original application did not disclose the precise features which later were incorporated into claim 1 by reference to a prior art document containing them, a precise and originally disclosed feature, namely the p53 sequence shown in figure 2 of document (21) has been introduced into claim 1 and other independent claims.

20. Moreover, the Respondents objected that neither example 2 nor example 4, where reference is made to document (21), refers to a method of diagnosis according to claim 1. As such diagnostic method is disclosed only in column 2 of the original application, under the heading "Summary of the Invention", where no reference to document (21) is made, the subject-matter of claim 1 violates Article 123(2) EPC.

The Board is convinced that the application as filed as a whole refers to diagnostic methods for detecting the loss of wild-type p53 genes, and therapeutic methods for supplying human wild-type p53 gene function to a cell. As acknowledged by the Board with regard to lack of sufficient disclosure of the main request and of auxiliary requests I to III (see above), and as agreed

by the Respondents, the original application discloses five different sequences as being wild-type p53 sequences. One thereof is the sequence referred to in the independent claims of auxiliary request IV. The introduction of this sequence into the claims by reference to document (21) does not therefore contravene the requirements of Article 123(2) EPC.

21. By defining the wild-type p53 gene sequence in the claims as corresponding to the sequence disclosed in document (21) the patent has not been amended in such a way as to extend the protection conferred (Article 123(3) EPC.

Clarity (Article 84 EPC)

22. The Respondents referred to decision T 11/89 of 6 December 1990 and argued that according to the case law of the Boards of Appeal a reference to a prior art document is not a technical feature and is not appropriate for determining the scope of a claim. Therefore, claim 1, which is not clear by itself, but only when read in combination with document (21), violates the requirements of Article 84 EPC.

23. Decision T 11/89 is concerned with a patent application referring to a group of chemical compounds defined in claim 1 by a formula (I). The claim comprises a disclaimer reading: *"...mit Ausnahme der in der EP-A-0 133 530 offenbarten Naphtyridinon-Derivate der allgemeinen Formel I."*

Thus the reference to a prior art document is used to disclaim a not precisely defined group of compounds

disclosed therein. The competent Board found that a disclaimer formulated in this way does not allow to clearly define the scope of the claim which therefore violated Article 84 EPC.

24. This is different from the present situation, where the skilled reader has no difficulty to define the scope of the claim. Claim 1 refers to a diagnostic test which requires knowledge of the wild type p53 gene sequence. This sequence is defined as being identical to the sequence shown in document (21).

25. Moreover, the Respondents objected that claim 1 refers to *"the wild-type p53 gene sequence"* shown in document (21) while the cited document discloses in Figure 2 the human and mouse p53 cDNAs. Claim 1 lacks clarity, firstly because a cDNA is a different entity than a genomic DNA, and secondly because document (21) discloses more than one sequence.

26. When considering a claim, one should rule out interpretations which are illogical or which do not make technical sense. One should try to arrive at an interpretation of the claim which is technically sensible and takes into account the whole disclosure of the patent (Article 69 EPC). The claim must be construed by a mind willing to understand not a mind desirous of misunderstanding (cf decision T 396/99 of 19 November 2001, ultimate paragraph of section 3.5).

27. Claim 1 refers to a diagnostic method practised on an isolated human tissue sample comprising the detection of loss of wild type p53 genes. Use of mouse DNA as reference sequence would not make technical sense.

28. The claim refers to *"the wild type p53 gene sequence"* shown in document (21). The Board, while being aware of the difference between a cDNA sequence and a genomic DNA sequence, takes the view that it is clear to a skilled person willing to understand claim 1, that this term defines the human sequence shown in Figure 2 of document (21), as in the contextual meaning of the language as used in the technical field concerned, the term *"gene sequence"* is not normally used to define an entire gene but rather the protein encoding exons thereof. The description of the application as filed, column 10, lines 55 to 57 reads: *"First, p53 cDNA probes detecting exons spread over 20,000 base pairs (including all protein encoding exons)..."*. This passage is immediately followed by the citation of, among others, document (21).

29. In consequence, the Board is convinced that the claims of auxiliary request IV meet the requirements of Article 84 EPC.

Patentable inventions (Article 52(4) EPC)

30. None of the claims refers to a diagnostic or therapeutic method practised on the human or animal body, which are not regarded as patentable inventions according to Article 52(4) EPC.

Sufficiency of disclosure (Article 83 EPC)

31. The Respondents argued that the diagnostic method according to claim 1 is not sufficiently disclosed. The method relies on the analyses of the p53 gene sequence

in a cell of a tissue sample and the determination whether or not this sequence is identical to the p53 gene sequence disclosed in document (21). Such method will give rise to a large number of wrong positive results, as the wild-type sequence shown in document (21) is only one of a number of human wild-type sequences, others being for instance disclosed in documents (16), (22) and (23). Therefore, many samples containing one of this other p53 wild-type sequences will wrongly be considered to contain neoplastic tissue.

32. The Board does not share the Respondents' view. Claim 1 refers to a method comprising the comparison of the p53 gene contained in a tissue sample with a defined reference sequence, namely the p53 wild-type sequence shown in document (21). Thus, the patent contains sufficient information allowing a skilled person to carry out the claimed method according to the requirements of Article 83 EPC.

The same applies to claims referring to a method for supplying human wild-type p53 gene function to a cell have lost this function, by introducing into the cell in vitro a gene having the sequence shown in document (21).

The point raised by the Respondents, namely if a method according to claim 1 reliably can be used for the diagnosis of a neoplastic tissue (see point (31) above), refers to the question if the problem underlying the patent is solved. This does not have to be considered under Article 83 EPC but under Article 56 EPC.

Inventive step (Article 56 EPC)
Remittal to the first instance (Article 111(1) EPC)

33. The Board, as a consequence of the substantial amendments to the claims according to auxiliary request IV, proposed in the appeal procedure, has decided that this request meets the requirements of Articles 52(4), 83, 84, 123(2) and 123(3) EPC.

Examination of inventive step has not been carried out by the Opposition Division, as all requests before them were found not to meet the requirements of the EPC for other reasons (see section IV above).

In the present case, in the light of the substantive amendments made to the claims, the Board considers it justified and appropriate to have this issue examined by two instances.

Thus, the Board at its discretion under Article 111(1) EPC remits the case to the Opposition Division for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution on the basis of claims 1 to 34 of the auxiliary request IV filed on 27 May 2005.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey