Datasheet for the decision of 21 December 2006

Case Number: T 0936/02 - 3.3.04
Application Number: 93912127.3
Publication Number: 0635068
IPC: C12Q 1/68
Language of the proceedings: EN

Title of invention:
Amplification of human MDM2 gene in human tumors

Patentee:
THE JOHNS HOPKINS UNIVERSITY

Opponent:
Roche Diagnostics GmbH

Headword:
Human MDM2 gene/JOHN HOPKINS UNIVERSITY

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 88, 89, 100(b), 123(2), (3)

Keyword:
"Added subject-matter (no)"
"Priority (yes)"
"Novelty, inventive step, sufficiency of disclosure (yes)"

Decisions cited:
G 0002/98, T 1002/92, T 0609/02

Catchword:
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Case Number: T 0936/02 - 3.3.04

DECISION
of the Technical Board of Appeal 3.3.04
of 21 December 2006

Appellant: Roche Diagnostics GmbH
(Opponent)
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
7 August 2002 concerning maintenance of the
European patent No. 0635068 in amended form.

Composition of the Board:
Chair: M. Wieser
Members: B. Claes
          G. Weiss
Summary of Facts and Submissions

I. The appeal was lodged by the opponent (appellant) against the interlocutory decision of the opposition division stating that European patent No. 0 635 068, claiming priority from US 867840 filed on 7 April 1992 (P1) and US 903103 filed on 23 June 1992 (P2), could be maintained in amended form pursuant to Article 102(3) EPC on the basis of claims 1 to 34 (all designated Contracting States except ES) and claims 1-41 (ES) of the main request filed with letter dated 4 January 2002.

II. Claims 22, 23 and 29 to 32 for all designated Contracting States of the patent as granted read as follows:

"22. A method of treating in vitro a neoplastic cell or a human cell having neoplastic potential, comprising: administering to a cell in vitro a therapeutically effective amount of an inhibitory compound which interferes with the expression of human MDM2 gene."

"23. The method of claim 22, wherein expression of the human MDM2 gene is inhibited by administering antisense oligonucleotides or by administering triple-strand forming oligonucleotides which interact with DNA."

"29. A polypeptide consisting essentially of a portion of p53, said portion comprising amino acids 13-41 of p53; or amino acids 1-41 of p53; or amino acids 13-57 of p53; or amino acids 1-50 of p53; said polypeptide capable of binding to human MDM-2."
"30. A method for inhibiting in vitro the growth of tumor cells which contain a human MDM2 gene amplification, comprising: administering in vitro a polypeptide as defined in claim 29, or a DNA-molecule which expresses a polypeptide as defined in claim 29 to tumor cells which contain a human MDM2 gene amplification."

"31. A polypeptide of claim 29 for use in a method for inhibiting the growth of tumor cells which contain a human MDM2 gene amplification."

"32. A DNA molecule as defined in claim 30 for use in a method for inhibiting the growth of tumor cells which contain a human MDM2 gene amplification."

III. The patent had been opposed as a whole on the basis of the grounds of opposition in Article 100(a) EPC combined with Articles 54 and 56 EPC, i.e. lack of novelty and inventive step, and in Article 100(b) EPC.

IV. The present decision refers to the following documents:

(1) Fakharzadeh et al. (1991), EMBO J., Vol. 10, No. 6, pages 1565-1569

(2) Momand et al. (1992), Cell, Vol. 69, pages 1237-1245

(4) EP-A-0 475 623

(5) Unger et al. (1992), EMBO J., Vol. 11, No. 4, pages 1383-1390
V. The board expressed its preliminary opinion in a communication dated 8 June 2006.

VI. With letter of 17 November 2006, the appellant submitted the new document (4) and argued on the patentability of the claimed subject-matter.

VII. Oral proceedings were held on 21 December 2006 during which the appellant presented documents (5) to (7). The respondent (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 7 for all designated Contracting States except ES and claims 1 to 5 for the designated Contracting State ES filed at the oral proceedings. The appellant requested that the decision under appeal be set aside and the patent be revoked.

VIII. Claims 1 to 7 for all designated Contracting States except ES of the respondent's request read as follows:

"1. A method of treating in vitro a human neoplastic cell or a human cell having neoplastic potential, comprising: administering to a cell in vitro a therapeutically effective amount of an inhibitory compound which interferes with the expression of human MDM2 gene wherein expression of the human MDM2 gene is inhibited by administering antisense oligonucleotides
or by administering triple-strand forming oligonucleotides which interact with DNA."

"2. A method for identifying compounds which interfere with the binding of human MDM2 to human p53, comprising:
binding a predetermined quantity of a first human protein which is detectably labelled to a second human protein;
adding a compound to be tested for its capacity to inhibit binding of said first and second proteins to each other;
determining the quantity of the first human protein which is displaced from or prevented from binding to the second human protein;
wherein the first human protein is MDM2 and the second human protein is p53 or the first human protein is p53 and the second human protein is MDM2."

"3. The method of claim 2, wherein one of said two human proteins is fixed to a solid support."

"4. The method of any of claims 2 or 3, wherein an antibody specifically immunoreactive with said second human protein is used to separate first human protein bound from unbound first human protein."

"5. A method for inhibiting in vitro the growth of tumor cells which contain a human MDM2 gene amplification, comprising:
administering in vitro a polypeptide consisting of a portion of p53, said portion comprising amino acids 1-50 of p53; said polypeptide capable of binding to human MDM-2 or a DNA-molecule which expresses said
polypeptide to tumor cells which contain a human MDM2 gene amplification."

"6. A polypeptide as defined in claim 5 for use in a method for inhibiting the growth of tumor cells which contain a human MDM2 gene amplification."

"7. A DNA molecule as defined in claim 5 for use in a method for inhibiting the growth of tumor cells which contain a human MDM2 gene amplification."

Claims 1 to 5 for the designated Contracting State ES of the respondent's request were identical to claims 1 to 5 for the request for all designated Contracting States except ES.

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

Priority

- Document (2) was prior art pursuant Article 54(2) EPC for claims 2 to 7 of the respondent's request. It was however not contained in the prior art for the subject-matter of claim 1. Although formal support could be identified in document (P2) for the subject-matter of claims 2 to 4, the document lacked an enabling disclosure in this respect as neither of the priority documents disclosed compounds which interfere with the binding of human MDM2 and p53 and were devoid of any hint as to the nature and structure of such compounds. Furthermore, no such
compound had ever been identified by the method of claim 2.

- The principles as established in decision T 609/02 of 27 October 2004, that if the description of a patent specification provides no more than a vague indication of a possible medical use for a chemical compound yet to be identified, later more detailed evidence cannot be used to remedy the fundamental insufficiency of disclosure of the subject-matter, applied to the present case.

**Sufficiency of disclosure**

- The same arguments relating to the issue of the validity of the priority for the subject-matter of claims 2 to 4 applied under Article 100(b) EPC.

- The patent does not sufficiently disclose how the compounds as defined in claims 5 to 7, i.e. proteins or DNA molecules, can inhibit the growth of tumor cells seeing that these compounds cannot pass the cell membrane which is necessary to be active in the claimed inhibition of growth.

**Inventive step**

- Closest prior art for the embodiments of claims 1 to 4 was document (1) which described the cloning of the murine MDM2 gene. The cloning of the human MDM2 gene and therefore the subject-matter of claims 1 to 4, was rendered obvious to the skilled person by the teaching of this document.
Closest prior art for the embodiments of claims 5 to 7 was document (2) which described the inhibition of p53 mediated transcription activation (transactivation) by means of a tight complex formation with the MDM2 gene product (see abstract, last sentence) suggesting that some aspects of cellular proliferation which are controlled by p53 can be abrogated by MDM2 (see page 1237, last 5 lines of the Introduction). p53 and the MDM2 gene played reciprocal roles in regulating each other, depending on their levels or other possible variables (protein modification, different spliced forms of the MDM2 gene, etc.) which was consistent with the fact that amplified copies of the MDM2 gene in murine cells result in a 20-to 50-fold increase in MDM2 RNA and confer an enhanced tumorigenic potential upon such cells (see page 1243, left hand column, lines 1 to 9).

The skilled person would combine the teaching of document (2) with the p53 fragments as disclosed in either of documents (5) or (7) and test the fragments as a potential inhibitor of tumor cell growth upon administration. Accordingly, the subject-matter if claims 5 to 7 lacked an inventive step.

X. The submissions by the respondent, as far as they are relevant for the present decision, may be summarised as follows:
Priority

- Document (2) was prior art pursuant to Article 54(2) EPC only for claims 5 to 7 of the request.

- At page 9 lines 15 to 27, and in particular at lines 17 to 19, the second priority document (P2) disclosed that "Antibodies specific for epitopes on hMDM2 or p53 which are involved in the binding interaction will interfere with such binding". Therefore, priority application (P2) can not be considered devoid of any suggestions as to the nature and structure of possible MDM2 and p53 binding inhibitors.

- The present case differed from the case underlying decision T 609/02 (supra).

Sufficiency of disclosure

- The arguments under the heading priority applied also to the requirements of Article 100(b) EPC.

- The appellant had not provided any evidence to substantiate the argument that the patent does not sufficiently disclose how the compounds as defined in claims 5 to 7 can inhibit the growth of tumor cells. Furthermore, at the relevant date, there were plenty of methods known to the skilled person in the art for introducing proteins and/or DNA molecules into cells. Examples thereof where e.g. injection, transfection or by transporter molecules.
Inventive step

- The problem to be solved was the provision of a target for therapy of tumorigenic cells. The patent taught the human MDM2 and p53 interaction as such a target. The prior art did not render this interaction and the aspects thereof which where claimed obvious.

Reasons for the Decision

Admission into the proceedings of late filed documents

1. In proceedings before the Boards of Appeal new facts and evidence which go beyond the facts and evidence presented in the notice of opposition should only be admitted into the proceedings if prima facie there are good reasons to suspect that such late-filed material would prejudice the maintenance of the European patent (see e.g. decision T 1002/92, OJ EPO 1995, 605). According to the established practice of the Boards of Appeal new facts and evidence, e.g. prior art documents filed shortly before, or during, the oral proceedings may not in principle be admitted into the opposition appeal proceedings, if they would lead to undue delay in the proceedings.

2. In the present case document (4) was filed just over one month before and documents (5) to (7) were filed in the course of the oral proceedings before the board. They relate to polypeptides which were subject-matter of claim 29 as granted, i.e. the human p53 protein and portions thereof. Furthermore, documents (5) to (7) are
mentioned in the patent at page 11 (see lines 31, 32 and 38). The respondent agreed with the introduction of the new documents into the proceedings. The board, accordingly, did not to make use of its discretion pursuant to Article 114(2) EPC and admitted documents (4) to (7) into the proceedings.

Amendments – Articles 84 and 123(2),(3) EPC

3. Since the requirements of Article 84 EPC are not a ground of opposition and the ground of opposition under Article 100(c) EPC has not been invoked within the framework of the present opposition proceedings, the examination of the requirements of Articles 84 and 123(2) EPC of the claims of the respondent's request is restricted to amendments made over the patent in its granted form.

4. Claim 1 for all designated Contracting States constitutes a combination of independent claim 22 and dependent claim 23 as granted, whereas claims 2 to 4 for all designated Contracting States are identical to claims 26 to 28 as granted. Claim 5 for all designated Contracting States corresponds to claim 30 as granted thereby referring to the polypeptide alternative last mentioned in claim 29 as granted. Claim 6 and 7 for all designated Contracting States except ES correspond to claims 31 and 32 as granted, respectively, and refer to the polypeptide or DNA-molecule as now defined in claim 5 (see above).

5. Accordingly, the amendments to the claims as granted contained in the respondent's request comply with the requirements of Article 123(2) EPC. Furthermore, since
the amendments constitute restrictions of the claimed subject-matter in comparison with that in the granted patent, the requirements of the Article 123(3) EPC have been met. The appellant has not raised any objections in this respect.

6. The appellant has neither disputed the clarity or any other requirements pursuant to Article 84 EPC of the claims. The board thus has no reason to address these issues.

Novelty

7. The appellant has furthermore not disputed the novelty of the subject-matter of the claims of the respondent's request. Accordingly, the board has no reason to address this issue either.

Priority

8. Since document (2) was published between the filing date of the second priority document (P2) and the filing date of the European patent application, the effective dates of the claims of the respondent's request pursuant to Article 89 EPC need to be determined.

9. The appellant has agreed that the effective date of claim 1 was at least the second date of priority. The effective date of claims 5 to 7 was however the filing date. The respondent agreed with these findings and the board sees no reason to disagree therewith.
10. In accordance with opinion G 2/98 of the Enlarged Board of Appeal, the requirement for claiming priority of the "same invention", referred to in Article 87(1) EPC, means that the priority of a previous application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole.

11. In the present case the appellant has not contested the fact that the subject-matter of the invention as defined in claim 2 can be derived directly and unambiguously from the priority applications as a whole, in particular from claim 32 of the second priority application (P2). The board therefore sees no necessity to examine this issue.

12. However, and in view of the established principle in the case law of the boards of Appeal that a priority document must also disclose the invention claimed in the subsequent application in such a way that a skilled person can carry it out (see Case Law of the Boards of Appeal of the EPO, section IV.B.3), the appellant has argued that the priority applications insufficiently discloses the subject-matter of claim 2. Accordingly, the relevant date for claims 2 to 4 was the filing date of the European patent application.

In particular, the priority documents did not disclose compounds which interfere with the binding of human MDM2 and p53 and were devoid of any hint as to the nature and structure of such compounds. The fact that at the day of oral proceedings still no such compound
had been identified by the method of claim 2, demonstrated that the identification of such compounds constituted an undue burden. The subject-matter of claim 2 was therefore not sufficiently disclosed. Furthermore, the principles as established in decision T 609/02 of 27 October 2004, that if the description of a patent specification provides no more than a vague indication of a possible medical use for chemical compound yet to be identified, later more detailed evidence cannot be used to remedy the fundamental insufficiency of disclosure of the subject-matter, applied to the present case.

12.1 The board cannot concur with the argumentation of the appellant. The subject-matter of claim 2 is a method for the identification of compounds which inhibit the binding of two identified and characterised proteins. At page 9 lines 15 to 27, and in particular at lines 17 to 19, the second priority document (P2) discloses that "Antibodies specific for epitopes on hMDM2 or p53 which are involved in the binding interaction will interfere with such binding". Hence the board considers that priority application (P2) can not be considered devoid of any suggestions as to the nature and structure of possible MDM2 and p53 binding inhibitors.

Furthermore the board notes that, contrary to the claim underlying the decision T 609/02 (supra), which related to so called "reach-through" or "down-stream" aspects of chemical compounds which still needed to be identified and of which the structural nature was therefore still unknown, the claim under investigation in the present case is a method for identifying compounds which interfere with the binding of two
defined proteins. The board therefore considers that the principles established for claims to the medical use of chemical compound yet to be identified are not relevant for the present case.

13. In view of the above considerations, the effective date pursuant to Article 89 EPC for claims 1 to 4 is before and for claims 5 to 7 of the respondent's request after the publication date of document (2). Document (2) is therefore not prior art pursuant to Article 54(2) EPC for the subject-matter of claims 1 to 4.

Sufficiency of disclosure

14. During the oral proceedings the appellant has reiterated the arguments relating to the issue of the validity of the priority for the subject-matter of claims 2 to 4 in the framework of objections under Article 100(b) EPC. The board considers however that for the analogous reasons as given in point 12 above, the appellant's arguments cannot substantiate a lack of sufficiency of disclosure.

15. The appellant has furthermore argued that the patent did not sufficiently disclose how the compounds as defined in claims 5 to 7, i.e. proteins or DNA molecules, can inhibit the growth of tumor cells seeing that these compounds cannot pass the cell membrane which is necessary to be active in the claimed inhibition of growth.

16. The board notes that the appellant has not provided any evidence to substantiate this argument. Furthermore, the appellant has not contested that, at the relevant
date, there were plenty of methods known to the skilled
person in the art for introducing proteins and/or DNA
molecules into cells, e.g. by injection, transfection
or with the help of transporter molecules.

17. In view of the above considerations, the board is
satisfied that the subject-matter of claims 1 to 7
complies with the requirements of Article 100(b) EPC.

Inventive step

18. For assessing whether or not a claimed invention
involves an inventive step as defined in Article 56 EPC,
the Boards of Appeal consistently apply the "problem
and solution" approach, which requires as a first step
the identification of the closest prior art. In
accordance with established case law of the boards of
appeal the closest prior art is generally a teaching in
a document conceived for the same purpose or aiming at
the same objective as the claimed invention and having
the most relevant technical features in common, i.e.
ideally requiring the minimum of structural
modifications to arrive at the claimed invention.

Claim 1

19. The subject-matter of claim 1 is a method of treating a
human cell which is neoplastic or has neoplastic
potential whereby the treatment comprises the
administration of a therapeutically effective amount of
an inhibitory compound which interferes with the
expression of human MDM2 gene.
19.1 Document (1) characterises the murine MDM2 gene as being evolutionary conserved, as having tumorigenic potential activated by amplification and as playing a predicted role in mechanisms of cellular growth (see abstract and page 1566, right hand column last full paragraph, page 1567, left hand column, lines 6 to 8). In particular, the enhanced expression of the gene is associated with tumorigenic potential of mouse and rat cells in which the gene was amplified (see e.g. Title).

19.2 The board agrees with the appellant that document (1) represents the closest prior art for the assessment of inventive step of the method of treatment of the subject-matter of claim 1. In the light of this closest prior art the problem to be solved by the invention according to claim 1, is the provision of a method for treating human cells which are neoplastic or have neoplastic potential.

19.3 The appellant has not disputed that the subject-matter of claim 1 solves this problem. Also the board sees no reason to deny that the problem is solved by the claimed subject-matter.

19.4 It needs to be established whether or not the administration of a therapeutically effective amount of an inhibitory compound which interferes with the expression of human MDM2 gene, i.e. an antisense oligonucleotides or a triple-strand forming oligonucleotides which interact with DNA, to a cell was rendered obvious by the state of the art to the skilled person when embarking to solve the above formulated problem.
19.5 Document (1) describes the characterisation of the murine MDM2 gene and correlates its amplification with the tumorigenic potential of mouse and rat cells and predicts a role in mechanisms of cellular growth. Neither document (1) alone, nor any of the other cited documents relevant under Article 54(2) EPC describe or suggest a treatment of tumorigenic cells or cells having a tumorigenic potential by administration of an inhibitor of MDM2 gene expression, let alone the treatment of such human cells with inhibitors of the human MDM2 gene.

20. The appellant has argued that, based on the teaching in document (1), the characterisation and cloning of the human MDM2 gene was rendered obvious to the skilled person. Furthermore, seeing that document (1) disclosed the correlation of the MDM2 gene expression due to gene amplification and tumorigenic potential of cells, the targeted inhibition of the expression of the MDM2 gene as a method of treatment of tumorigenic cells constituted mere routine experimentation of the skilled person.

20.1 The formulation of the claimed solution starting from the teaching of document (1) requires at least the following three steps; i) the cloning of the human MDM2 gene, ii) the recognition of the potential of human MDM2 gene expression inhibitors in the treatment of human tumorigenic cells or human cells with a tumorigenic potential and iii) the formulation of suitable human MDM2 gene expression inhibitors. As can be taken from point 19.5 above, at least step ii) was not rendered obvious by any of the cited documents contained in the prior art pursuant to Article 54(2)
EPC. Hence, and independently of the assessment whether or not the first step i), i.e. the cloning of the human MDM2 gene based on the teaching of document (1) involved an inventive step or not, the subject matter of claim 1 was not rendered obvious to the skilled person.

20.2 In view of the above considerations the method of treatment of claim 1 was not rendered obvious to the skilled person by the prior art. The subject-matter of claim 1 therefore involves an inventive step.

Claims 2 to 4

21. Claim 2 is directed to a method for identifying compounds which interfere with the binding of human MDM2 to human p53.

21.1 The closest prior art for the invention of claim 2 is represented by document (4) which describes the human p53 gene and protein and methods for utilising p53 cDNA and p53 gene products in the suppression of the neoplastic phenotype and methods for treating cells based on these compounds to suppress tumorigenesis (see page 2, lines 46 to 58).

21.2 Accordingly, the problem to be solved by invention is the provision of compounds which bind to human p53.

21.3 Neither document (4) itself nor one of the other cited documents relevant under Article 54(2) EPC, describe or suggest an interaction of p53 with MDM2. Therefore, the binding of human p53 and human MDM2 as disclosed in the
The patent was not rendered obvious to the skilled person by the prior art.

21.4 The subject matter of claim 2, and of its dependent claims 3 and 4, involves therefore an inventive step.

Claims 5 to 7

22. Claim 5 is directed to a method for inhibiting the growth of tumor cells which contain a human MDM2 gene amplification by administration of a polypeptide consisting of a portion of human p53 comprising amino acids 1-50 of p53 and being capable of binding to human MDM-2 or a DNA-molecule which expresses said polypeptide. The subject-matter of claim 6 is the p53 protein portion and claim 7 is directed the DNA molecule both as defined in claim 5 and claimed for use in a method for inhibiting the growth of tumor cells which contain a human MDM2 gene amplification.

22.1 Document (2), which is prior art pursuant to Article 54(2) EPC for claims 5 to 7 (see point 13), describes the inhibition of p53 mediated transcription activation (transactivation) by means of a tight complex formation with the MDM2 gene product (see abstract, last sentence) suggesting that some aspects of cellular proliferation which are controlled by p53 can be abrogated by MDM2 (see page 1237, last 5 lines of the introduction). Document (2) states that the available evidence might suggest that p523 and the MDM2 gene play reciprocal roles in regulating each other, depending on their levels or other possible variables (protein modification, different spliced forms of the MDM2 gene, etc.), and consistent therewith that
amplified copies of the MDM2 gene in murine cells result in a 20-to 50-fold increase in MDM2 RNA and confer an enhanced tumorigenic potential upon such cells (see page 1243, left hand column, lines 1 to 9).

22.2 The problem to be solved is the provision of compounds for use in a method for inhibiting the growth of tumor cells which contain a human MDM2 gene amplification.

22.3 The board is satisfied that the subject-matter of claims 5 to 7, the administration of a polypeptide consisting of a portion of human p53 comprising amino acids 1-50 of p53 and being capable of binding to human MDM-2 or a DNA-molecule which expresses said polypeptide, constitutes a solution to the above problem. In particular example 7 of the patent identifies the NH₂-terminial 50 amino acids of p53 as comprising the MDM2 binding region.

22.4 It therefore needs to be analysed whether or not the prior art renders the use of the p53 amino acid 1-50 fragment in the treatment of tumor cells containing a human MDM2 gene amplification obvious to a skilled person.

22.5 Document (4) discloses methods for utilising p53 cDNA and p53 gene products in the suppression of the neoplastic phenotype and methods for treating cells based on these compounds to suppress tumorigenesis. Documents (5) to (7) disclose p53 deletion mutants which identify the transcription activation domain of p53. In particular the documents identify amino acids 1-42, document (5); amino acids 20-50, document (6);
amino acids 1-73, document (7) as the p53 transactivation domain.

22.6 The board notes however that none of these documents identify these peptides or the transactivation domain in general as a potential inhibitor of tumor cell growth upon administration. Accordingly, none of these documents render the use of the transactivation domain of p53 as a growth inhibitor of tumor cells which contain a human MDM2 gene amplification obvious.

23. In view of the above considerations the subject-matter of claims 1 to 7 for all designated Contracting States except ES and claims 1 to 5 for ES of the respondent's request involves an inventive step.
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 with the order to maintain the patent on the basis of claims 1 to 7 for all designated Contracting States except ES and claims 1 to 5 for the designated Contracting State ES filed at the oral proceedings and description and figures yet to be adapted thereto.

The Registrar

The Chair

P. Cremona

M. Wieser