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**Datasheet for the decision
of 21 February 2008**

Case Number: T 0125/07 - 3.3.08

Application Number: 95940906.1

Publication Number: 0782709

IPC: G01N 33/574

Language of the proceedings: EN

Title of invention:

Detection and treatment of cancer

Applicant:

Moro, Ricardo J.

Headword:

alpha-fetoprotein receptor/MORO

Relevant legal provisions:

EPC Art. 123(2)

Relevant legal provisions (EPC 1973):

EPC Art. 54(1), 56, 83, 84

Keyword:

"Sole request - added subject-matter (no)"
"Sufficiency of disclosure (yes)"
"Novelty and inventive step (yes)"

Decisions cited:

-

Catchword:

-



Case Number: T 0125/07 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 21 February 2008

Appellant: Moro, Ricardo J.
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 25 July 2006
refusing European application No. 95940906.1
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: F. Davison-Brunel
Members: P. Julià
T. Karamanli

Summary of Facts and Submissions

I. European patent application No. 95 940 906.1 published as WO 96/09551 with the title "Detection and treatment of cancer" was refused by the examining division pursuant to Article 97(1) EPC 1973.

II. Claim 1 of the main request refused by the examining division read as follows:

"1. A method for detecting or monitoring of a cancer in a patient comprising the steps of

obtaining a biological sample from a body of a patient,

introducing anti-(alpha-fetoprotein receptor)-antibodies or alpha-fetoprotein to the biological sample of the patient to bind anti-(alpha-fetoprotein receptor)-antibodies or alpha-fetoprotein to the alpha-fetoprotein receptor in the biological sample; and

determining the level of alpha-fetoprotein receptor in the biological sample which has reacted with the anti-(alpha-fetoprotein receptor)-antibody or alpha-fetoprotein to detect the presence of a cancer in the patient."

III. The examining division considered the main request and the first to the fifth auxiliary requests then on file to lack inventive step over the closest prior art document D1 (R. Moro et al., Tumor Biol., 1993, Vol. 14, pages 116 to 130) in combination with the general knowledge of the skilled person. In its opinion,

document D1 suggested a method for diagnosis of cancer based on detecting the presence of the α -fetoprotein receptor (AFP_r) in serum samples by immunoassay. The claimed method differed from the method suggested in document D1 in that the level (concentration) - and not only the presence - of AFP_r was determined, a measure which was obvious to the skilled person. Claim 1 of auxiliary requests 1 to 5 only differed from claim 1 of the main request in ways which had also been suggested in document D1 or were conventional in the technical field considered and/or within the customary practice of the skilled person.

- IV. The applicant (appellant) filed an appeal against the decision of the examining division, paid the appeal fee and submitted a statement setting out the grounds of appeal together with a new main request and ten new auxiliary requests.
- V. The examining division did not rectify the contested decision and referred the appeal to the board of appeal (Article 109 EPC 1973).
- VI. The board sent a communication as annex to the summons to oral proceedings stating its preliminary, non-binding opinion.
- VII. In a letter dated 21 January 2008, the appellant replied to the board's communication, withdrew all previous requests and filed one new request.
- VIII. Oral proceedings took place on 21 February 2008. During the oral proceedings, the appellant withdrew its previous request and filed a new sole request.

IX. Claim 1 of appellant's **sole request** filed at oral proceedings read as follows:

"1. A method for detecting the presence of a cancerous tumor in a human patient, comprising the steps of

obtaining a biological sample of a body fluid from the patient, and

introducing labeled anti- α -fetoprotein receptor antibodies (anti-AFPr antibodies) to the biological sample to bind soluble α -fetoprotein receptor (AFPr) in the biological sample, and

determining the level of reaction of soluble AFPr in the biological sample with the anti-AFPr antibodies to detect the presence of the cancerous tumor in the patient;

wherein the body fluid is blood, saliva or serum and the tumor is in the ovary, lymph node, limb, soft tissue, stomach, abdomen, uterus, bladder, prostate, rectum, colon, pelvis, brain, lung, liver, kidney or bone."

Claims 2 to 8 were directed to particular embodiments of claim 1.

X. The appellant's arguments, filed in writing or submitted during the oral proceedings, insofar as relevant to the present decision, may be summarised as follows:

Sole request

Article 56 EPC 1973

Document D1 disclosed antibodies specific for the α -fetoprotein receptor (AFPr) and the presence of circulating soluble AFPr in fetal material (cord serum) and in tumor-contacting fluids (pleural effusions and cancerous cytosols). Although it suggested that soluble AFPr could serve as a cancer marker, this suggestion was merely speculative and had to be read in the light of the common general knowledge. It was not to be expected from document D1 nor from any other prior art that soluble AFPr would leave the tumor medium *in vivo*, migrate through tissues to the bloodstream and thence to other remote body fluids. A fortiori it could not have been envisaged that it would retain its binding capacities to the antibodies and be present in blood or serum at an assayable concentration despite an excess of AFP in bloodstream, thus providing a successful remote cancer detection system.

On the contrary, there were scientific reasons to cast doubts on the use of AFPr in a cancer assay. Firstly, AFPr had a glycan binding site, with a complex and variable glycosylation pattern which caused unpredictability across populations and even across different cells within an individual's body. Secondly, the natural binding partner of AFPr, i.e. AFP, was found in serum at high levels, exceeding the soluble AFPr produced by few cancer cells. Since AFP inhibited the anti-AFPr antibody reaction with soluble AFPr, an antibody-based assay based on soluble AFPr was not expected to work. Thirdly, the breast cancer studied in document D1 was not predictive of cancers generally.

And fourthly, AFPr was perceived as merely a detail in the AFP pathway, AFP then being a well established cancer marker.

If, nevertheless, document D1 was taken as the closest prior art, the objective technical problem was to be seen in the improvement of the suggested AFPr-based tumor detection method. The solution was the claimed remote detection method, i.e. the detection of organ tumors via a body fluid sample separated from the organ by the bloodstream, which provided an improved specificity, sensitivity and universality, as shown by the evidence on file.

Neither document D1 nor any other prior art provided the skilled person with a reasonable expectation of success. The extracellular release of soluble AFPr was not part of the normal physiological role of AFPr in cell development. *In vivo*, dead cancer cells were attacked by microphages which destroyed the membrane-attached AFPr and prevented its release. Moreover, AFPr was more insoluble than other oncofetal antigens such as CEA and AFP, so natural release of soluble AFPr from a tumor *in vivo* was not reasonably expected.

The umbilical cord serum - described in document D1 as containing soluble AFPr - was not similar to normal human serum and a conclusion of obviousness could not be derived from the presence of AFPr therein. Firstly, cord serum AFPr was fetal in origin and not cancerous. Secondly, AFPr levels in cord serum were in excess of the expected levels in normal human serum because AFPr (along with AFP) expression sharply decreased in the

first weeks of life. Thirdly, the physiological role of fetal AFPr was different from that of AFPr in normal or tumor cells and no meaningful comparisons could be made between fetal, normal or tumor AFPr release, soluble AFPr turnover and replenishment in serum, etc. Finally, cord serum AFPr had no remoteness from any cancer site.

The pleural effusions - described in document D1 as containing soluble AFPr - were from lung-metastases of a mammary cancer patient and they had no remoteness from the cancer site. These effusions were massively loaded with expressed cancer markers from the (AFP-negative) lung-metastases and the soluble AFPr had undergone no passage into patient's blood and thus it had not yet been diluted out by binding to the AFP expected to be present in the blood. The presence of AFPr in pleural effusions could not provide a reasonable expectation that AFPr could serve as a remote cancer detection marker, let alone for the very specific cancer types mentioned in the claims.

No conclusions could be derived from the presence of cellular AFPr in the specific tumor cells mentioned in document D1, since nothing was known on the release of soluble AFPr to the specific body fluids mentioned in the claims and they were not remote from the cancerous origin as required in the claimed method.

- XI. The appellant (applicant) requested that the decision under appeal be set aside and that a patent be granted on the basis of his sole request filed at oral proceedings of 21 February 2008.

Reasons for the Decision

1. The present decision was taken after the revised European Patent Convention ("EPC 2000") entered into force on 13 December 2007. Since the European patent application in suit was pending at that time, the Board applied the transitional provisions in accordance with Article 7(1), second sentence, of the Act revising the EPC of 29 November 2000 and the Decisions of the Administrative Council of 28 June 2001 (Special edition No. 1, OJ EPO 2007, 197) and 7 December 2006 (Special edition No. 1, OJ EPO 2007, 89). Articles and Rules of the revised EPC and of the EPC valid until that time are cited in accordance with the Citation Practice (see the 13th edition of the European Patent Convention, page 4).

Sole request

Article 123(2) EPC and Articles 84 and 83 EPC 1973

2. No objections were raised by the examining division under these articles. The now claimed subject-matter, directed to a method for detecting the presence of a cancerous tumor in a human patient, is based on the detection of **soluble** α -fetoprotein receptor (AFP_r) and has been further limited by defining the **body fluids** (blood, serum or saliva) present in the biological sample used and the **cancerous organ tumors** detected.
3. The release of AFP_r into the body fluids, either by secretion or by passive diffusion after cell death, is described in paragraphs bridging pages 17 to 18 and 29 to 30 of the application as published, wherein the latter paragraph defines the circulating AFP_r as a

soluble protein. The assays described as appropriate for the claimed method require "*a free antigen (AFP receptor here)*" and they only work "*with soluble antigens*" (cf. paragraph bridging pages 34 and 35). The presence of soluble AFPr in blood or serum of human patients having the organ tumors mentioned in claim 1 finds a basis in Example #1 (Table I) and on page 31, lines 1 to 25, where it is also stated that "*a small amount of most of the serum proteins appears in saliva*".

4. The combination of soluble AFPr with the specific body fluids mentioned now in claim 1 directly defines the nature and character of the assay by characterizing both the product measured and its source. No ambiguity arises by the introduction of these features into the claim and they are also technically supported by the description of the application (Example #1, Table I).
5. The requirements of Article 123(2) EPC and Articles 84 and 83 EPC 1973 are thus fulfilled.

Article 54(1) EPC 1973

6. The examining division did not raise any objection for lack of novelty. In view of the prior art on file, the board does not see any reason to raise an objection in this respect. The requirements of Article 54(1) EPC 1973 are met.

Article 56 EPC 1973

7. In line with the decision under appeal, document D1, *supra*, is considered to be the closest prior art. This document discloses the production of monoclonal

antibodies (MAbs) against AFPr present on the cellular membrane of fetal and neoplastic cells. These MAbs inhibit the binding of AFP to the AFPr of several malignant cell lines and, conversely, an excess of AFP inhibits the MAb reaction. Reference is also made to preliminary results suggesting that anti-AFPr MAbs reduce the proliferation of those malignant cell lines. Document D1 further discloses a method of purification of AFPr that relies on the dissociation of the AFP-AFPr complexes in the presence of high KCl concentrations.

8. According to document D1, high cytoplasmic KCl concentrations might also facilitate the release of AFP, internalized as a complex with its membrane receptor, and *"the resulting free receptor could account, at least in part, for the receptor found in membrane-free materials such as cord serum, the pleural effusion from a metastatic mammary cancer and the cytosols"* (cf. page 126, right-hand column, last full paragraph). It is further stated that *"the presence of the AFP receptor in body fluids such as cord serum or the pleural effusion ... could be the result of an active excretion by cancer cells or just a consequence of cell death. In both cases, the presence of detectable amounts of AFP receptor in body fluids and particularly serum might prove useful for the diagnostic and follow-up of a wide range of malignancies"* (cf. page 128, right-hand column, full paragraph).

9. Starting from this closest prior art, the objective technical problem to be solved may be seen as putting into practice the suggested diagnostic method. The claimed method for detecting the presence of a cancerous tumor in a human patient which is performed

in blood, serum or saliva, solves this technical problem.

10. In the light of the explicit suggestion of document D1, the board has no doubts that it would be obvious for the person skilled in the art to look for soluble AFPr in the serum of human patients with tumor malignancies. In the present case, the key issue is thus to assess whether a reasonable expectation of success to find it there is also given (cf. "Case Law of the Boards of Appeal of the EPO", 5th edition 2006, II.D.6, page 132). The presence of soluble AFPr in the cytosols of fetal and neoplastic cells cannot confer any expectation to the skilled person since most intracellular proteins are not normally secreted. And, in any case, nothing is known in the prior art about a passive secretion (diffusion) or an active release of soluble AFPr, whether it be from normal fetal or adult human cells or from the cancerous tumor cell lines identified in document D1 as containing membrane-associated AFPr.

11. The presence of soluble AFPr in umbilical cord serum and in pleural effusions of a lung metastatic mammary carcinoma disclosed in document D1 could be regarded as providing some expectation that measuring AFPr in bodily fluids such as claimed could be used as a tumor marker. However, as argued by the appellant (cf. Section X *supra*), neither cord serum nor pleural effusions are in any way comparable to blood or serum, let alone saliva, of a human patient with an organ tumor and the former fluids do not have any predictive value for the latter.

12. The umbilical cord carries nourishment and oxygen from the placenta to the fetus and returns waste products to the placenta from the fetus. Cord serum is thus closely associated with - and particular to - the fetus and it might be enriched in (or alternatively, deprived of) substances that otherwise might be absent (or present) in normal human serum. Since the actual mechanisms underlying the presence of soluble AFP_r in cord serum are unknown (active AFP_r release or passive AFP_r diffusion from fetal cell death, low degradation and high stability of fetal AFP_r in cord serum, etc.), let alone their possible similarities or differences to those of cancerous tumors, no expectations can be derived therefrom.

13. The pleura is defined as a membrane with inner and outer layers (the former covering the lungs and the latter lining the rib cage and diaphragm), producing a fluid that allows the lungs to move in and out smoothly. Pleural effusions are formed when too much of this fluid builds up between the two layers (pleural cavity). These effusions are thus closely associated with - and particular to - the pleura. The local accumulation of a substance in those effusions is not predictive of its presence in serum since it depends on many factors (pleural lymphatic drainage, convection, transcytosis, diffusion, etc) and therefore, no expectations can be derived therefrom.

14. Even if, for the sake of argument, the release and/or diffusion of soluble AFP_r from cancerous tumor cells into the bloodstream of a human patient could be derived from the presence of soluble AFP_r in umbilical cord serum or in pleural effusions, doubts would still

remain as to whether the level of AFP_r would be high enough for significant detection (AFP_r stability) and whether the presence of endogenous AFP ligand would interfere with this detection (AFP_r availability). Moreover, there is no indication on file that could have led the skilled person to expect the release and/or diffusion of AFP_r and the presence of stable and measurable amounts of soluble AFP_r for each and every one of the specific organ tumors mentioned in claim 1.

15. To conclude, the suggestion made in document D1 is considered as merely speculative and without any technical basis. Hence, no reasonable expectation of success can be derived therefrom - nor from other prior art on file - and therefore, the claimed subject-matter is inventive (Article 56 EPC 1973).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent with the following claims and a description to be adapted:

Claims: No. 1 to 8 received at oral proceedings of 21 February 2008.

The Registrar:

The Chairwoman:

A. Wolinski

F. Davison-Brunel