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Datasheet for the decision of 16 October 2007

Case Number: T 0531/05 - 3.3.04

Application Number: 97915954.8

Publication Number: 0929694

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
Detection of extracellular tumor-associated nucleic acid in blood plasma or serum using nucleic acid amplification assays

Applicant:
THE PENN STATE RESEARCH FOUNDATION

Opponent:
-

Headword:
Extracellular tumor-associated nucleic acid/PENN STATE RESEARCH FOUNDATION

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0531/05 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 16 October 2007

Appellant: THE PENN STATE RESEARCH FOUNDATION
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 9 December 2004 refusing European application No. 97915954.8 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chair: U. Kinkeldey
Members: B. Claes
H. Preglau

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division refusing European patent application 97915954.8, based on international patent application PCT/US97/04010 which was published as WO97/34015 with the title "Detection of extracellular tumor-associated nucleic acid in blood plasma or serum using nucleic acid amplification assays", pursuant to Article 97(1) EPC *inter alia* for the reason that the subject-matter of claims 1 to 6 of the main request filed with letter of 23 March 2004 lacked an inventive step (Article 56 EPC).

Claim 1 of the main request read:

" 1. A method for identifying whether or not an asymptomatic human is at risk of developing colorectal cancer, pancreatic cancer, lung cancer, or gastric cancer, the method comprising the steps of:

a) extracting extracellular DNA from blood obtained from the asymptomatic human;

b) subjecting the extracted extracellular DNA to an amplification method designed to produce, if the extracted extracellular DNA includes mutant K-ras DNA, an amplified fragment of mutant K-ras DNA;

c) assaying for the presence of the amplified fragment of mutant K-ras DNA; and

d) if the amplified fragment of mutant K-ras DNA is present, thereby identifying the asymptomatic human as being at risk of developing colorectal cancer, pancreatic cancer, lung cancer, or gastric cancer."

Claims 2 to 6 were dependent thereon.

II. The board summoned oral proceedings to take place on 16 October 2007.

III. With letter dated 17 September 2007 the appellant filed an auxiliary request 1 and 2.

Claim 1 of auxiliary request 1 read:

"1. A method for detecting the presence of precancerous cells for colorectal cancer, pancreatic cancer, lung cancer, or gastric cancer, in an asymptomatic human, the method comprising the steps of:

a) extracting extracellular DNA from blood obtained from the asymptomatic human;

b) subjecting the extracted extracellular DNA to an amplification method designed to produce, if the extracted extracellular DNA includes mutant K-ras DNA, an amplified fragment of mutant K-ras DNA;

c) assaying for the presence of the amplified fragment of mutant K-ras DNA; and

d) if the amplified fragment of mutant K-ras DNA is present, thereby identifying the pressure of precancerous cells for colorectal cancer, pancreatic cancer, lung cancer, or gastric cancer."

Claim 1 of auxiliary request 2 read:

"1. A method for detecting the presence of precancerous cells for colorectal cancer, pancreatic cancer, lung cancer or gastric cancer, in a human, the method comprising the steps of:

a) extracting extracellular DNA from blood obtained from the asymptomatic human;

b) subjecting the extracted extracellular DNA to an amplification method designed to produce, if the extracted extracellular DNA includes mutant K-ras DNA, an amplified fragment of mutant K-ras DNA;

c) assaying for the presence of the amplified fragment of mutant K-ras DNA; and

d) if the amplified fragment of mutant K-ms DNA is present, thereby identifying the pressure of precancerous cells for colorectal cancer, pancreatic cancer, lung cancer, or gastric cancer."

IV. Oral proceedings took duly place on 16 October 2007.

V. The following documents are referred to in the present decision:

Kopreski Declaration: filed by the applicant/appellant during the examination proceedings with letter of 7 April 2003.

(1): Sorensen et al. (1994), Cancer Epidemiology, Biomarkers & Prevention, Vol. 3, pages 67 to 71.

(6): Sorensen (2000), Clinical Cancer Research, Vol.6, pages 2129-2137.

VI. The appellant's arguments relating to inventive step can be summarised as follows:

– The claimed subject-matter constituted an easy and inexpensive alternative to the existing cancer prescreening programs of asymptomatic individuals for detecting premalignancy which involved

inter alia cumbersome, invasive and/or unpleasant diagnostic methods.

– It could be taken from the declaration of the inventor Dr Kopreski ("Kopreski declaration") that, although prior to the invention the detection of K-ras mutations in the plasma or serum of cancer patients could be detected, it was totally unexpected to detect mutated K-ras DNA amongst extracellular DNA present in the blood of an individual having no discernable signs of cancer. There were a number of reasons for this. First, unlike non-hematopoietic premalignant tissue cancer cells were often found circulating in the blood. Secondly, cancers had a substantially greater tumor extent than their precursor premalignant tissue which were also often separated from the blood supply by a so-called basement membrane, so that there was no expectation that non-hematopoietic tissue would provide sufficient mass to yield detectable amounts of extracellular DNA in the blood. Thirdly, even if extracellular DNA from premalignancy stages of cancer had access to the blood, it was unexpected that the extracellular DNA levels would be sufficient for detection.

– Even in post-published document (6) the author of document (1) still reported that the detection of mutated K-ras in the blood of humans suggested that it is probable, or even almost certain that the patient has cancer.

– In view of the lack of expectations the subject-matter of the claimed invention involved an inventive step.

VII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 6, filed with letter dated 23 March 2004 (main request) or claims 1 to 3 of the first or second auxiliary request, filed with letter dated 17 September 2007.

Reasons for the Decision

1. The present decision is concerned with the question whether the subject-matter of claim 1 of the main request and claim 1 of each of the two auxiliary requests involves an inventive step (Article 56 EPC).

2. For assessing inventive step, 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.

3. The invention in claim 1 aims at identifying whether or not an asymptomatic human is at risk of developing colorectal cancer, pancreatic cancer, lung cancer or gastric cancer, i.e. cancers generally known to be associated with particular K-ras oncogene mutations.

The board therefore considers that, as also suggested by the appellant, the closest prior art for the subject-matter of claim 1 are the diagnostic tests used in existing cancer screening programs of asymptomatic individuals for early detection of premalignancy which involve *inter alia* cumbersome, invasive and/or unpleasant *in situ* diagnostic methods.

4. The problem to be solved by the invention of claim 1 can therefore be defined as the provision of an alternative to these existing cancer prescreening programs of asymptomatic individuals which is for the patient more comfortable.

5. Claim 1 solves this problem by means of a method involving the testing for the presence of mutant K-ras DNA sequences in the extracellular DNA of the blood of such asymptomatic patients, such presence being indicative for the risk.

6. Document (1) teaches that in blood plasma and serum of human patients with malignant tumors, in the specific case pancreatic adenocarcinoma, mutated K-ras oncogene DNA sequences can be detected. To this end the document discloses a method for the detection of mutated K-ras oncogene DNA sequences in the blood. The author concludes on page 70, left hand column, lines 22 to 26, that the presence of mutated K-ras DNA sequences in blood is, *a priori*, presumed to be a highly specific indication for the presence of a premalignant, or much more likely, a malignant tumor of any of multiple common types. It has not been disputed that the basic method steps (a) to (c) of the method of claim 1 are identical to the method steps of the detection method

as disclosed in document (1). Document (1) therefore provides the skilled person with a simple blood test for detecting mutated K-ras DNA sequences in blood of humans, its presence being indicative for the presence of a premalignancy or malignancy related to the detected mutated K-ras oncogene.

7. The relevant question is therefore whether or not, and with a view to solve the above technical problem, it was obvious to the skilled person to embark on testing asymptomatic persons, independently whether they had been previously identified as having a risk for developing one of the referred to cancers, by applying the method steps as claimed for the presence of mutated K-ras sequences in their blood.

8. The board is convinced that to the skilled person who is taught by document (1) that in blood plasma and serum of human patients harbouring malignant, and possibly premalignant, tumors mutated K-ras oncogene DNA sequences can be detected, it is obvious that the detection method as described in document (1) can be used to test asymptomatic humans for the presence of mutated K-ras oncogene DNA sequences in their blood, thereby being indicative of a risk to develop cancers known to be associated with such mutations.

9. The appellant has argued that - as could be taken from the declaration of the inventor Dr Kopreski ("Kopreski declaration") - at the relevant date of the present application it was totally unexpected to the skilled person that it was possible to detect mutated K-ras DNA amongst extracellular DNA present in the blood of an individual having no discernable signs of cancer in

view of the fact that first, non-hematopoietic premalignant cells did not circulate in the blood, secondly, precursor premalignant tissue was often separated from the blood supply by a so-called basement membrane and thirdly, even if extracellular DNA from premalignancy stages of cancer had access to the blood, it was unexpected that the extracellular DNA levels would be sufficient for detection. The appellant further argued that even in post-published document (6) the author of document (1) still reported that the detection of mutated K-ras in the blood of humans suggested that it is probable, or even almost certain that the patient had cancer.

10. The board considers however that the statement in document (1) that presence of mutated K-ras DNA sequences in blood is, a priori, presumed to be a highly specific indication for the presence of a premalignant, or much more likely, a malignant tumor of any of multiple common types renders it obvious to the skilled person to try to test in e.g. in such humans who, although being asymptomatic, would qualify for existing cancer screening programs of asymptomatic individuals for early detection, for the presence of K-ras mutations in the blood. The possible considerations submitted by the appellant which may have made the skilled person hesitant concerning the applicability of the test method to asymptomatic persons do not constitute a well researched and documented technical prejudice, but rather the expression of sound scientific modesty of the clinician in the field which would not prevent the skilled person from embarking on solving the problem by the claimed subject-matter.

11. In view of the above considerations, the subject-matter of claim 1 of the main request lacks inventive step (Article 56 EPC).

12. Claims 1 of auxiliary requests 1 and 2 are directed to detecting the presence of precancerous cells for K-ras associated cancers in the blood of humans. The referred to "precancerous cells" of these claims correlate to the premalignant cells as referred to in document (1). The board therefore considers that the facts and arguments leading to the finding of lack of inventive step for the subject-matter of claim 1 of the main request also apply to the subject-matter of these claims. Accordingly, also the subject-matter of claims 1 of auxiliary requests 1 and 2 lack inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

P. Cremona U. Kinkeldey