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BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

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File Number: T 36/90 - 3.3.2

Application No.: 82 302 937.6

Publication No.: 0 067 642

Title of invention: Detection of malignant tumor cells

Classification: C12N 15/00

# D E C I S I O N
of 7 October 1991

Applicant: Bogoch, Samuel, Dr.

Headword: Tumor cells/BOGOCH

EPC Article 56

Keyword: "Inventive step - (no), obvious provision of products having known properties"

## Headnote

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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number : T 36/90 - 3.3.2**

# D E C I S I O N
## of the Technical Board of Appeal 3.3.2
## of 7 October 1991

**Appellant :** Bogoch, Samuel, Dr.
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**Decision under appeal :** Decision of Examining Division of the European Patent Office dated 30 June 1989 refusing European patent application No. 82 302 937.6 pursuant to Article 97(1) EPC.

**Composition of the Board :**

**Chairman :** P.A.M. Lançon
**Members :** U.M. Kinkeldey
F. Benussi

## Summary of Facts and Submissions

I. European patent application No. 82 302 937.6, published under No. 0 067 642, was refused by the Examining Division.

The refusal was based on 14 claims, the broadest independent product Claim 8 being worded as follows:

"8. A test kit for the diagnosis of cancerous or malignant tumor cells in a cell collection which comprises a monoclonal anti-cancer Recognin."

II. The ground given for the refusal was that the application did not meet the requirements of Article 56 EPC. The subject-matter of Claims 1 to 14, although novel, lacked an inventive step having regard to the disclosures of EP-A-0 007 214 (document (1)) or EP-0 015 755 (document (2)) in combination with the teaching of a further document (3), published by Milstein in Scientific American, October 1980, Vol. 243, pages 56 to 64. Documents (1) and (2) individually disclosed polyclonal antibodies and processes for the detection of cancer tumours. It was known from (3) to prepare hybridomas secreting monoclonal antibodies. The author of (3) had also shown a synergistic effect of polyclonal antibodies leading to their cytotoxicity and thus explained the non-cytotoxicity of "the purified" monoclonal antibodies. Accordingly, the skilled man in the field of immunology having knowledge of the teachings of these prior art documents was well able to prepare monoclonal antibodies according to the teaching of document (3), and use them for the in vitro or in vivo detection of cancerous or malignant cells.

IV. The Applicant lodged an appeal against this decision and paid the fees. Further, a written statement setting out the grounds for the appeal was filed on 2 November 1989.

A set of new Claims 1 to 18 were attached to the grounds of appeal. Independent Claims 1, 7 and 13, read as follows:

"1. A process for the quantitative detection of the presence in vitro of cancerous or malignant tumor cells in a cell collection regardless of the cell type of the cancerous or malignant cells, which comprises applying to the cell collection in vitro a specific monoclonal anti-cancer Recognin, which preferentially attaches to cancerous cells and can thereby be detected by attached visible or signal-emitting means, the Recognin comprising a product, derived from cancerous tumor tissue or cells, characterised by forming a single line precipitate with its specific antibody in quantitative precipitin tests and Ouchterlony gel diffusion tests, being soluble in water and aqueous solutions having an acid or neutral pH, and insoluble at alkaline pH, having a spectrophotometric absorption peak wavelength of 280 mμ and a molecular weight of from 3,000 to 25,000, and further characterized by having an amino-acid residue composition characterized by high proportions of glutamic and aspartic acids and high ratios of glutamic and aspartic acids to histidine, detecting the presence of cancerous cells by means of the visible or signal-emitting means, and determining quantitatively the number of cells labelled by the monoclonal anti-cancer Recognin.

7. A test kit for the quantitative detection of cancerous or malignant tumor cells in a cell collection regardless of the cell type of the cancerous or malignant cells which

comprises a monoclonal anti-cancer Recognin labelled with a visible or signal-emitting means.

13. A monoclonal anti-cancer Recognin for use in vitro or in vivo in the quantitative detection of cancerous or malignant tumor cells regardless of the cell type of the cancerous or malignant tumour cells."

As regards Claim 13, it is to be noted that an independent product claim of this kind, namely directed to a monoclonal antibody as such was filed for the first time; also the definition of this monoclonal antibody to be used in the quantitative detection of tumour cells.

Upon request of the Appellant oral proceedings were summoned and postponed by the Board. In a letter dated 21 June 1991 he informed the Board that he would not attend the oral proceedings and therefore requested that the outcome of the Appeal be determined on the basis of the submissions which were already before the Appeal Board.

V. The Appellant's arguments in the statement of appeal may be summarised as follows:

(a) Documents (1) and (2) were concerned with cytotoxic polyclonal antibodies which could be used to detect the presence of cancerous cells. The polyclonal antibodies according to this prior art, however, could not be used in a quantitative diagnostic test for cancerous cells in a fluid suspension since they kill the cells.

(b) Although document (3) described the synergistic effect of polyclonal antibodies and thereby explained the non-cytotoxicity of purified

monoclonal antibodies, the reference would be considered to be rather speculative regarding the potential use of monoclonal antibodies. In particular (3) does not describe diagnostic testing in general and there is also no suggestion that:

(i) monoclonal antibodies could be used in a process for the quantitative detection of the presence in vitro of cancerous or malignant tumour cells; or

(ii) that a general cancer antibody could be prepared. In fact everything in (3) would have led to the opposite assumption of cell-type specific monoclonal antibodies.

(c) The monoclonal anti-cancer Recognins according to the application were the first general transformation antibodies which would label and thus permit staining of most or all types of cancer cells. The other antibody technologies available in 1981 or now were based on the knowledge of the exact cell type that is malignant. Specific antibodies which stain a specific cancer cell were known and the diagnostic test often failed if a specific anti-cancer antibody was used to detect metastases. When radio-labelled monoclonal or polyclonal antibodies were injected into the body to localise cancer cells in the body by radiographic means the cell type was generally not known and the test would frequently fail with all other antibodies, but would succeed with anti-cancer Recognin antibodies.

VI. The Appellant requests that the decision under appeal be set aside and that a patent be granted on the basis of Claims 1 to 18 filed on 2 November 1989.

Reasons for the Decision

1. The appeal is admissible.

2. Amendments (Article 123(2) EPC)

The Board sees no formal objections to the newly filed Claims 1 to 18.

Detailed explanations can be left in abeyance since the application fails for other reasons.

3. Problem and solution

3.1 The closest state of the art is document (2) which is concerned with anti-cancer Recognins being polyclonal antibodies, for use in the detection of cancerous or malignant tumour cells. Document (2) describes the production of Malignin, Astrocytin, Recognin L and M and their characterisation by the determination of their aminoacid composition (Examples 1-5).

Further the production of so called "target", being immobilized Malignin, Astrocytin or Recognin L and M, is also described (Example 6) as well as the production of polyclonal fast target attaching globulin (F-TAG) and slow target attaching globulin (S-TAG), the use of which in the in vitro detection of malignant cells in biological fluids or by immunofluorescence in histology section, i.e. in a collection of cells is exemplified (Examples 8 and 9). In Example 14 a signal emitter such as a dye or a radio-active label is bound to TAG.

Reference to in vitro detection of cancerous or malignant cells in a collection of cells can also be found in the description, cf. page 1, lines 9-13, page 10, lines 27-33, page 13, lines 30-36, page 14, lines 2-11 and page 15, lines 15-25. According to (2) these polyclonal anti-cancer Recognins are cytotoxic, cf. page 14, lines 21-25. Since these antibodies destroy the cells, their use is limited to the detection of cancerous cells, for example by immunofluorescence as demonstrated in (2). A quantitative measurement of the cancer event was only possible by quantitative antibody-antigene precipitations, wherein the antigene, providing knowledge about a more or less developed tumour growth is the Recognin molecule as such (see for example page 1, lines 9 to 13). It was not possible to make a quantitative detection of the tumour cells themselves.

3.2 In relation to the above prior art document (2), the technical problem to be solved was the improvement of the quantitative measurement of cancer events.

3.3 The solution according to the application consists in the provision of a monoclonal anti-cancer Recognin as set out in Claim 13.

The Board is convinced that the examples of the application, in particular Examples 14 and 15 supply sufficient and plausible evidence that the problem has been solved, i.e. that monoclonal anti-cancer Recognins have been prepared and permit a quantitative detection of cancerous or malignant tumour cells regardless of the cell type of the cancerous or malignant tumour cells.

4. Novelty (Article 54 EPC)

None of the prior art documents discloses a monoclonal anti-cancer Recognin, which is thus novel.

5. Inventive step (Article 56 EPC)

5.1 As set out above under point 3.1, document (2) describes Recognin antibodies which can be used in vitro or in vivo in the non-quantitative detection of cancerous tumour cells regardless of the cell type of the tumour cells (cf. also Example 9). These antibodies are produced by a multiplicity of cell clones resulting in a multiplicity of individual antibodies in a serum. As a consequence they are defined as polyclonal.

5.2 For purposes of inventive step the relevant question is now whether the skilled person having knowledge of this closest state of the art and being guided by the above defined technical problem could have been aware from his common general knowledge that the replacement of polyclonal anti-cancer Recognin by monoclonal anti-cancer Recognin could make the desired properties and effects available. A similar case has already been decided by a Board of Appeal (T 499/88 of 11 January 1990, unpublished), such that the replacement of polyclonal antibodies by monoclonal antibodies in an otherwise identical process, making use of the known advantages of monoclonal antibodies was considered as to be obvious. In the present case, however, a product claim is also at issue.

5.3 Monoclonal antibodies and their preparation are described in general in Article (3) published by Cesar Milstein who, together with G. Köhler, did in 1975 the famous milestone work in the field of monoclonal antibodies having a pre-defined specificity. Document (3) can be considered a review article summarising the essentials in this field between 1975 and 1980. Since the monospecificity of said antibodies from hybridomas has thrown new light on some

well-known effects resulting from antigen-antibody reactions, the author of (3) has put particular weight on the explanation of this phenomena.

5.4 As an example that monospecificity has revealed some unsuspected effects reference is made in document (3) to the binding of different antibodies to neighbouring sites on the same antigen which is an important factor in the formation of complement and rupture of a cell membrane. A synergistic effect was discovered by measuring the cell killing activity of culture mediums of antibody-secreting hybridomas. No cytotoxic activity could be found when testing the supernatants of hybridomas containing monoclonal antibodies (cf. page 62, right column). Having regard to the disclosure in this document, in general the non-cytotoxicity of monoclonal antibodies was taught to those skilled in the art.

5.5 In view of the well known cell fusion techniques and cell cloning methods described in general in document (3), (cf. pages 60/61) it is apparent that at the priority date of the present application the skilled person was basically familiar with the preparation of monoclonal antibodies. As the facts stand, the Board has no reason to believe that the Appellant was confronted with any particular difficulties in the present case.

5.6 Accordingly, once polyclonal anti-cancer Recognins were known, their cytotoxicity established and furthermore it was known that monoclonal anti-bodies show no cytotoxic activity the next logical and obvious step in order to solve the technical problem was to provide monoclonal anti-cancer Recognins.

5.7 Since also at the priority date of the present application the commercially available spectrometer for carrying out cytofluorography used in research laboratories were capable to detect the actual number of cells in a fluid suspension, it was only a matter of ordinary skill to adopt and adjust the spectrometer when using a monoclonal anti-cancer Recognin in vitro in the quantitative detection of tumour cells. The submission of the Appellant that it was not expressis verbis stated in (3) that monoclonal anti-bodies could be used in a process for the quantitative detection of the presence in vitro of cancerous tumour cells, is therefore not persuasive in view of the familiarity of the skilled person in the field of immunology with fluorescence spectroscopy and its application.

5.8 The Appellant's further argument also fails that there is no suggestion in (3) that a cancer antibody could be prepared which is not specific to a certain kind of tumour cells but rather can detect tumour cells of different types and that everything in (3) leads to the opposite assumption of cell type specific monoclonal antibodies. Document (2) clearly states this particular property of polyclonal anti-cancer Recognin.

A compound lacking inventive step over certain disclosures in the state of the art cannot be rendered patentable in view of non-obviousness over other disclosures (T 164/83, OJ EPO 1987, 149).

5.9 In the present case, it was clear to those skilled in the art that the polyclonal antibodies known from (2) also have the characteristics of general transformation antibodies, (cf. Example 13). It is indeed not the specificity which distinguishes polyclonal antibodies from

monoclonal antibodies, (see for example document (3), page 58, test tube antiserum and the test tubes clone 1 to clone 4), but rather the type of the population of these different antibodies and their way of preparation. Therefore, the Board does not share the Appellant's opinion that there was not, in 1981, nor is there now any antibody other than the ones described in the present application, which will label and thus permit staining of most or all types of cancer cells, because they are already state of the art according to document (2).

5.10 In the present case, it is the knowledge about the whole class of polyclonal anti-cancer Recognins described in document (2) in connection with the precise knowledge about the desired property here in question, namely to be non-cytotoxic, derivable from document (3) which renders the solution of the problem according to Claim 13 obvious.

5.11 Accordingly, Claim 13 cannot be allowed under Article 56 EPC.

5.12 Since the Appellant withdrew their request for oral proceedings and in addition had sufficient opportunity to state his case in written form (Article 113 EPC), the Board sees no reason to continue the written procedure.

The purpose of oral proceedings is to discuss with the parties all the subject-matter which is required for the decision. However, a party who does not make use of this opportunity cannot appeal under Article 113(1) EPC, on the basis that he was unable to comment on certain grounds of the decision which might have been the subject-matter of the said oral proceedings.

5.13 Thus, as the facts stand, nothing patentable can be seen in the other claims and since there is no auxiliary request, Claims 1 to 12 and 14 to 18 share the fate of Claim 13.

**Order**

**For these reasons, it is decided that:**

The appeal is dismissed.

The Registrar: The Chairman:

P. Martorana P. Lançon