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Datasheet for the decision of 9 May 2023

Case Number: T 0416/18 - 3.3.08

Application Number: 12176466.6

Publication Number: 2543739

IPC: C12Q1/68

Language of the proceedings: EN

Title of invention:
CONSENSUS CODING SEQUENCES OF HUMAN COLORECTAL CANCERS

Patent Proprietor:
JOHNS HOPKINS UNIVERSITY

Opponent:
Strawman Limited

Headword:
Human colorectal cancers/JOHNS HOPKINS UNIVERSITY

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 13(2)

Keyword:
Inventive step - main request and auxiliary request 1 (no)
Admittance of late-filed evidence and lines of argument - (no)

Decisions cited:

Catchword:

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Beschwerdekammern

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Case Number: T 0416/18 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 9 May 2023

Appellant: (Opponent)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
Representative:	Reekmans, S. van Someren, P. Arnold & Siedsma Bezuidenhoutseweg 57 2594 AC The Hague (NL)
Respondent: (Patent Proprietor)	JOHNS HOPKINS UNIVERSITY 100 North Charles Street 5th Floor Baltimore, MD 21201 (US)
Representative:	Tombling, Adrian George Withers & Rogers LLP 2 London Bridge London SE1 9RA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 12 December 2017 concerning maintenance of the European Patent No. 2543739 in amended form**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	D. Pilat
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 2 543 739 is based on European patent application No. 12 176 466.6, a divisional application of the earlier European patent application No. 07811279.4. The patent was opposed on the grounds of Article 100(a) in conjunction with Articles 54 and 56 EPC, and of Article 100(b) and (c) EPC. The opposition division held that the main request filed on 10 October 2016 met the requirements of the EPC.

II. The opponent (appellant) lodged an appeal against the decision of the opposition division, requesting that the decision under appeal be set aside and the patent be revoked in its entirety.

III. The patent proprietor (respondent) replied to the appeal, requesting inter alia that the appeal be dismissed and the patent be maintained on the basis of the main request, or alternatively on the basis of the first auxiliary request filed with its reply to the grounds of appeal.

IV. In a communication under Article 15(1) RPBA, the parties were informed of the board's provisional opinion on the issues of the case.

V. Both parties replied to the board's communication. The respondent filed a new version of document A6 ("full copy").

VI. Claim 1 of the main request reads as follows:

"1. A method of diagnosing colorectal cancer in a human, comprising the steps of:

determining in a test sample relative to a normal sample of the human, a somatic mutation in *KRAS* gene or its encoded mRNA or protein, said mutation being Kl17N;

identifying the sample as colorectal cancer when the somatic mutation is determined."

VII. Claim 1 of the first auxiliary request reads as follows:

"1. A method of diagnosing colorectal cancer in a human, comprising the steps of:

determining in a test sample relative to a normal sample of the human, a somatic mutation in *KRAS* gene or its encoded mRNA or protein, said mutation being Kl17N;

identifying the sample as colorectal cancer when the somatic mutation is determined, wherein the test sample is a colorectal tissue sample or a suspected colorectal cancer metastasis and the normal sample is a colorectal tissue sample."

VIII. The following documents are referred to in this decision:

A2: Ogino S. *et al.*, Journal of Molecular Diagnostics, Vol.7(3) pages 413 to 421, 2005

A3: Lièvre A. *et al.*, Cancer Res., 66(8), pages 3992 to 3995, 2006

A5: Higinbotham K.G. *et al.*, Molecular Carcinogenesis, Vol.5, pages 136 to 139, 1992

A6: Kerr, Workman: New Molecular Targets for Cancer Chemotherapy, excerpt of Chapter 6, CRC Press, 1994

A7: Bos J.L., Cancer Research, Vol.49, pages 4682 to 4689, 1989

IX. The arguments of the appellant, insofar as relevant to the present decision, may be summarised as follows:

Admittance and consideration of new lines of arguments based on the full copy of document A6

Document A6 in the proceedings was used as secondary document for inventive step by the appellant both in opposition and in appeal proceedings. The full copy of document A6 as well as the new arguments submitted with respondent's response to the board's communication were late filed and should not be admitted.

Article 56 EPC

Document A2 represented the closest prior art. The method of claim 1 differed from that of document A2 in that somatic Kl17N codon mutant in exon 4 was used to detect cancer cells vs normal cells instead of the known mutant codons 12 or 13 from human KRAS exon 1. An unexpected technical effect could not be attributed to this distinguishing feature. The patent disclosed a screening assay but without singling out a specific mutation having any particular effect.

The technical problem had therefore to be formulated as the provision of an alternative method of diagnosing colorectal cancer in a human.

In the patent, the *KRAS* gene was a comparative gene containing a well documented hotspot but was not disclosed as a gene of the invention (patent application, paragraph [0069]).

Document A5 mentioned that human tumours had activating mutations in either of the two hotspot regions in any of the *ras* gene or with rare exception in codons 117 and 146. The same information was derivable from document A6.

The skilled person starting from the method disclosed in document A2 and faced with the technical problem of finding an alternative method of diagnosing colorectal cancer in a human would have turned to other activating mutations than those located in any of the ras genes in either of the two hotspot regions and would arrive at the claimed subject-matter without an inventive step.

X. The arguments of the respondent, insofar as relevant to the present decision, may be summarised as follows:

Admittance and consideration of new lines of arguments based on the full copy of document A6

Since the board in its preliminary opinion considered the teaching of document A6 to be relevant for the patentability of the claims, a full copy of document A6 was submitted to ensure that the teaching of the admitted excerpt was seen in its context.

Article 56 EPC

Document A2, the closest prior art, taught KRAS mutations at codons 12 and 13 but provided no teaching that KRAS had another K117N mutation being associated with colorectal cancer and that other mutations might be present in KRAS. The technical effect underlying the difference consisted of the detection of this mutation in KRAS in human colorectal cancer.

The method of claim 1 allowed the diagnosis of human colorectal cancer when the K117N mutation was detected in KRAS.

None of the documents A2, A5 and A6 taught or suggested that KRAS would be mutated at codon 117, let alone that KRAS having a K117N mutation would be associated with human colorectal cancer.

Starting from document A2 the skilled person faced with the technical problem identified above would have been confronted with a fishing expedition. None of the documents A2, A3 and A7 provided a motivation to look for a mutation other than those already detected in the KRAS gene.

Even if the skilled person would have detected the claimed mutation in KRAS, there was no disclosure of a statistical analysis to exclude that the mutation was a passenger mutation (patent, Example 4 and paragraph [0063]). Hence, there was no reasonable expectation that a mutation in KRAS at position 117 was indeed associated with human colorectal cancer.

XI. The final requests of the parties, in so far as relevant for the present decision, were:

The appellant requested that the decision under appeal be set aside and the patent be revoked.

The respondent requested that the appeal be dismissed and the patent be maintained on the basis of the main request, or alternatively on the basis of the first auxiliary request filed with its reply to the grounds of appeal. It further requested that a new version of document A6 ("full copy") be admitted.

Reasons for the Decision

Admittance and consideration of new lines of argument based on the full copy of document A6 (Article 13(2) RPBA)

1. As reaction to the board's communication pursuant to Article 15(1) RPBA, the respondent submitted a new version of document A6, namely a version comprising a full copy of Chapter 6 rather than just page 102 thereof as was on file. The respondent argued that this full copy of document A6 should be admitted because, since the board considered for the first time that document A6 was relevant for the patentability of the claims, there had been a change from the previous position taken by the opposition division as regards the relevance of document A6. The document A6 which was already in the proceedings was only an excerpt, whose teaching, if not read in context, could not be properly understood. Moreover, the appellant would not be presented with new information since they were certainly aware of the content of the full chapter from which they had isolated one page.

2. The board cannot accept this view, as the argumentation used in the board's preliminary opinion under Article 15(1) RPBA was essentially based on appellant's arguments on inventive step submitted during appeal proceedings and also in opposition proceedings (statement of grounds of appeal, page 14, last paragraph to page 15 first paragraph and notice of opposition starting on page 12). In its reply to the statement of grounds of appeal, the respondent referred to document A6 (page 4, fourth paragraph) but, while observing that only an extract of document A6 was on file, did not at that point consider it necessary to

file a full copy of document A6. As the board's communication contains a preliminary opinion based on issues raised by the parties and their arguments, that communication cannot be taken as a justification for submitting supplementary evidence at this late stage of the proceedings.

3. Even if the opposition division's decision did not indicate why document A6 was not relevant, the fact that the board does not follow this view and instead agrees with the appellant is one of the possible outcomes to be expected and cannot justify the admittance of respondent's new evidence and arguments based thereon at such a late stage of the proceedings. Hence the board considers that there were no exceptional circumstances justified with cogent reasons for the late submission of the new evidence and argumentation. Hence, the board decided not to admit them into the appeal proceedings.

Main request - Inventive step (Article 56 EPC) - Claim 1

4. The present invention relates to a method for diagnosing colorectal cancer in a human, wherein a somatic mutation in the KRAS gene or its encoded mRNA or protein, said mutation being codon K117N, is determined in a test sample (patent, paragraph [0005], claim 2).

5. Document A2 is the closest prior art. This has not been disputed. It discloses a pyrosequencing method for detecting known KRAS mutations, a technique that allows the detection of a minority of mutant KRAS alleles among abundant wild-type alleles (title, abstract). Using said technique, mutations at codons 12 and 13 of

KRAS were detected in patients who developed incident colorectal cancer (Figure 2 of document A2).

6. The difference between document A2 and the method of claim 1 is that the KRAS mutation to be detected according to claim 1 is the K117N. A technical effect, let alone an unexpected technical effect, associated with this difference is neither shown in the patent nor made plausible from the prior art. This has not been disputed.

7. Accordingly, the board agrees with the objective technical problem defined in the decision under appeal and formulated by the appellant, which is to provide an alternative method for diagnosing colorectal cancer in humans. The board moreover agrees that the method of claim 1, comprising the detection of a KRAS mutation K117N, solves this problem.

8. Thus, it remains to be assessed whether or not the skilled person starting from the disclosure in document A2 and faced with the problem defined above, would have arrived at the claimed solution in an obvious manner.

9. The board agrees with the respondent and the decision under appeal that neither document A2 nor any other available prior art documents disclose or point at the specific KRAS mutation K117N being associated with human colorectal cancer. However, since the technical problem is just the provision of alternative methods, there is no need for a pointer in the prior art. Moreover, documents A5 and A6 already pointed to mutations at K117 being linked to cancer.

Document A5, which focuses on mutations at codon 63 in a chemically induced rat renal tumour (title,

abstract), teaches that the incidence of mutations in genes of the *ras* family is high in carcinomas of the colon and explicitly mentions mutations in codon 117 (document A5, page 136 left column, first paragraph). On page 137, right column, first paragraph of the "Discussion" section, document A5 again mentions codon 117, among others, as a point mutation, albeit rare, associated with oncogenic *ras*. Document A6, on the other hand, teaches codon K117, as well as codons D116 and D119, as belonging to a so-called second set of "activating" *ras* mutations.

10. The skilled person starting from document A2 faced with the technical problem identified above could and would also have turned to documents A5 or A6 and select another/further KRAS somatic mutation for diagnosing human colorectal cancer. Since there was no need to achieve any technical effect beyond what was disclosed in prior art document A2 and there was no technical difficulties to be expected, the skilled person would have been motivated to use the method for diagnosing colorectal cancer in a human disclosed in document A2 but applying another specific somatic KRAS mutation mentioned in the prior art.

11. Thus, the combination of the method disclosed in document A2 with the teaching of documents A5 or A6 would have led the skilled person to consider the KRAS gene previously identified as a colorectal cancer gene, and the second set of "activating" mutations in positions 116, 117 or 119 within this gene (document A6), known to negatively affect guanine nucleotide binding activity thereby resulting in a constitutively activated protein. Without the need of a pointer, the skilled person would have selected one mutation, among all the equally possible mutations in this motif,

including mutation K117N, and accordingly would have arrived at the solution of claim 1 in an obvious manner. Consequently, the claimed subject-matter does not involve an inventive step.

12. The respondent argued that document A5 mentioned the mutation at codon 117 in a different context, namely in the context of reference [14], which related to oncogenes activated in a B6C3F1 hybrid mouse causing liver tumours. Hence document A5 referred to mutation at codon position 117 in association with the wrong species and the wrong disease. Moreover it neither specified the member of the *ras* gene family nor the specific mutation concerned.

The first reference to codon 117 in document A5 is on page 136, first paragraph of the Introduction section. This passage reads:

"*Mutational activation of ras in experimental animal tumors has also been extensively documented and reviewed (5). In both human and experimental tumors, with rare exceptions (codons 117 and 146), activating mutations occur in either of two hotspot regions in any of the ras genes: codons 12 and 13 in exon 1 or codons 59-61 in exon 2*."

13. The board notes that no difference is made between human and experimental tumours in the above statement. Secondly, it is explicitly stated that, apart from the two hotspot regions where the activating mutations typically occur, they can also occur at codons 117 and 146. Even if not explicitly referring to K-ras, the reference to "any of the *ras* genes" embraces all known *ras* gene family members, such as H-ras, K-ras and N-ras. Thus, from the above passage, the skilled person

would have derived that an activating mutation at codon 117 is to be expected in human tumours in any one of the ras gene family member, including KRAS.

14. The second reference to the mutation at codon 117 in document A5 is found in the first paragraph of the Discussion section (page 137, right-hand column) where it is associated with reference [14]. As is apparent from the title of reference 14 in the list of References (page 139, right column), this publication is related to oncogenes activated in a B6C3F1 hybrid mouse causing liver tumours. In view of the whole teaching of document A5 however, the skilled person would have no reason to consider that this teaching in the Discussion section was limited to the specific content of the cited publication it refers to. Clearly, said publication relates to animal models, from which the skilled person extrapolates to humans (in agreement with the first passage above, which explicitly mentions both experimental and human tumours).

15. As to document A6, the respondent argued that although K117 is explicitly mentioned (third paragraph), it was not assigned to the KRAS gene nor limited to K117N, let alone to the type of tumour in which this mutation occurs. Moreover, document A6 stated that, despite many mutations generated in vitro, only a few were found in human malignancies (last paragraph).

16. The third paragraph of document A6 reads as follows:

"*A second set of "activating" mutations - although they are very rarely found in human tumors - are those containing substitutions in the binding site of the guanine ring. Thus, mutation of either D116, Kl17, or D119 results in an appreciable reduction in the*

affinity of the protein for GDP- giving rise to a molecule which will exchange its nucleotide more rapidly, presumably spending more time in the active GTP-bound state.[38,39]"

17. From this passage, the skilled person would clearly derive that another set of "activating" mutations at position D116, Kl17, or D119, albeit very rarely found in human tumors, results in an appreciable reduction in the affinity of the protein for GDP. As discussed above in relation to document A5, the fact that this statement is supported by references 38 and 39 would not limit its teaching to the experimental setting of the publications cited as references. As to the respondent's argument that the specific mutations referred to in the second sentence of this paragraph were not necessarily the second set of "activating mutations" referred to in the first sentence, the board cannot share this view and notes that, even in the absence of the linking term "thus" at the beginning of the second sentence, this would be still the most logical interpretation.

The last paragraph of document A6 reads:

"*Despite the very large number of transforming Ras mutations which can be produced in vitro, relatively few have been identified in human malignancies. It is reasonable to suppose that this is either because certain areas of the gene may be considered "mutational hotspots" or, perhaps more probably, the NIH 3T3 focus assay does not always reflect the ability of the protein to promote oncogenesis in vivo*."

18. Contrary to the respondent's arguments, this passage does not raise doubts as to the value of the K117

mutation in a method for diagnosing human cancer; even if this mutation was one of the artificially generated mutations tested for transforming activity in NIH3T3 cells, still the skilled person would be motivated to test it further rather than discard it. Moreover, in the third paragraph of document A6, it is in fact disclosed as a mutation which is found, albeit rarely, in human tumours.

19. The respondent further argued that neither document A3, which related to KRAS mutations in colorectal cancer, nor document A7, which was a review of activating mutations in the three *ras* genes, H-ras, K-ras, and N-ras, disclosed or suggested that there could be mutations in KRAS other than at codons 12, 13, or 61 in human malignancies, let alone another specific K117N mutation in KRAS associated with colorectal cancer. Although this fact is undisputed, the contrary statement that no other mutations are to be expected in KRAS is incorrect and is inconsistent with the teaching of documents A5, A6, which refer to rare mutations events in human tumours in any of the *ras* genes at codon 117. The limited number of 30 and 60 samples tested and the conventional test assays and animal models might explain why the rare mutation position 117 was not detected in documents A3 or A7. Hence, the information allegedly missing from these documents cannot call into question the assertions made in two other independent prior art documents A5 and A6.

20. Finally, the respondent also argued that even if the mutation K117 could be detected, it would not be possible to determine whether or not it was a non-functional "passenger" mutation elicited by repeated rounds of cell division in the tumor or in the

progenitor stem cells. Reference was made to Example 4 of the patent.

21. The board disagrees. The statistical methods in the patent estimate the probability that the number of mutations observed in a given gene during a discovery and validation screen is greater than the one expected from the background mutation rate. The cancer mutation frequency (CaMP) score is the result of this analysis and reflects a cancer mutation prevalence for each gene. This score intends to distinguish between genes likely to contribute to tumorigenesis from those in which the mutations occur by chance (patent, paragraph [0040]). Since the KRAS gene is known in the art to be mutated in cancer tissues, there is no need for a skilled person to apply the statistical method of the patent to establish whether or not KRAS is involved in tumorigenesis. The CaMP score for KRAS is high and confirms this fact (patent, paragraph [0043] and Table 3 in Figure 7A).

22. Therefore, the subject-matter of claim 1 of the main request lacks an inventive step (Article 56 EPC).

First auxiliary request - Inventive step (Article 56 EPC) - Claim 1

23. Claim 1 of this request further specifies that the test sample is a colorectal tissue sample or a suspected colorectal cancer metastasis and the normal sample is a colorectal tissue sample. The respondent provided no arguments as to why this further limitation contributed for inventive step. The board also fails to see that this feature achieves a technical effect going beyond what is achieved by the claimed method of the main request. Hence, the objective technical problem for the

assessment of inventive step starting from the disclosure in document A2 representing the closest prior art is the same as for the main request.

24. Considering that document A2 discloses a method which involves identifying the sample as colorectal cancer when the somatic mutation is determined relative to a normal sample of the human (e.g. Figure 2 and its legend), the claimed method of the first auxiliary request lacks an inventive step for the same reasons as the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated