

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 34

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ILAN TSARFATY, JAMES H. RESAU, IAFA KEYDAR, DONNA L. FALETTO
and GEORGE F. VANDE WOUDE

Appeal No. 1999-0339
Application No. 07/903,588

ON BRIEF

Before ELLIS, MILLS and GRIMES, Administrative Patent Judges.
ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 103 from the examiner's final rejection of claims 1-4, all the claims pending in the application.

Claims 1 and 2 are illustrative of the subject matter on appeal and read as

follows:

1, A method for predicting the progression of a breast cancer comprising the steps of:

(a) determining one or more of met DNA abundance, met mRNA abundance, or Met protein abundance in normal breast tissue and in tumor breast tissue and (b) comparing the abundance of said met DNA, met RNA or Met protein in normal breast tissue with said met DNA, met RNA or Met protein in tumor breast tissue, wherein said normal and tumor tissue is from the same breast, and wherein a higher abundance of met DNA, met RNA, or Met protein in said normal tissue than in said tumor tissue indicates a poor prognosis.

2. A method according to claim 1, comprising the steps of:

(a) contacting a section from a breast tumor with an antibody reagent specific for Met protein under antibody binding conditions, wherein said section contains normal breast tissue and tumor tissue;

(b) determining the binding of the reagent to Met protein in said normal tissue and said tumor tissue; and

(c) comparing said binding of said reagent to Met protein in said normal tissue with said binding in said tumor tissue; wherein, greater binding of said reagent to said normal than to said tumor tissue indicates a poor prognosis.

The references relied upon by the examiner are:

Biéche et al., "Loss of heterozygosity on chromosome 7q and aggressive primary breast cancer", The Lancet, vol. 339, pgs. 139-143 (Jan. 1992).

Park et al., "Sequence of MET protooncogene cDNA has features characteristic of the tyrosine kinase family of growth-factor receptors", Proc. Natl. Acad. Sci., vol. 84, pgs. 6379-6383 (Sept. 1987).

The claims stand rejected as follows:

Appeal No. 1999-0339
Application 07/903,588

I. Claim 1 stands rejected under 35 U.S.C. § 103 as being unpatentable over Bièche.

II. Claims 2-4 stand rejected under 35 U.S.C. § 103 as being unpatentable over Bièche and Park.

We affirm Rejection I and reverse Rejection II.

BACKGROUND AND DISCUSSION

The human met proto-oncogene is a member of the tyrosine kinase family of oncogenes. Specification, p. 1, lines 11-15; Bièche, p. 140, col. 1, para. 1; Park, p. 6379, the abstract and col. 1, para. 1. The c-met gene is expressed in various tissues and cells, but the highest levels are said to be found in epithelial cells. Specification, p. 1, para. 2; Bièche, p. 140, col. 1, para. 1. Prior to this invention, investigators had determined that the c-met gene is located on chromosome 7q31 in primary breast tumor DNA. Bièche, p. 140, col. 1, para. 1.

As indicated by the claims, the present invention is said to be directed to methods of predicting the progression of a breast cancer by comparing the abundance of one or more of met DNA, met RNA or Met protein in normal breast tissue with the abundance of said DNA, RNA or Met protein in tumor breast tissue. According to the specification, a greater abundance of met DNA, met RNA or Met protein in normal breast tissue than in tumor breast tissue is indicative of a high likelihood of tumor metastasis. Specification, p. 5.

The examiner has premised his conclusion with respect to the obviousness of claim 1 on the teachings of Bièche.

To that end, we find that Bièche discloses studies wherein a c-met proto-oncogene probe (pmetH) which detects met gene sequences on chromosome 7q31, is used to analyze tumor and blood leukocyte DNA samples in patients with primary breast cancers. Bièche, p. 139, col. 1, para. 1, p. 140, cols. 1-2. The pmetH probe recognizes TaqI restriction fragment length polymorphisms (RFLP) of 7.5 kb (L fragment) and 4.0 kb (S fragment) in tumor and lymphocyte DNA of patients with primary breast cancer. Bièche, p. 140, cols. 1-2. Bièche found that of 245 patients, 81 were homozygous for the L fragment (LL genotype), 43 were homozygous for the S fragment (SS) and 121 were heterozygous (LS). Bièche, p. 140, col. 2, para. 1. Bièche analyzed blood leukocyte and tumor DNA from those patients who are heterozygous (LS) with the pmetH probe and found a loss of heterozygosity of the c-met proto-oncogene in 49 of the 121 (40.5%) patients. Id., para. 2; see also Figure 1. In follow-up studies, Bièche found that the loss of heterozygosity was associated with “significantly higher risk of relapse (55% vs 21%) and of death (41% vs 15%)” and “reduced metastasis-free (p+ 0.00022) and overall (p+0.0036) survival” compared with patients who did not have the DNA deletion. Bièche, p. 142, col. 1., para. 2 and p. 141, sentence bridging cols. 1-2. Bièche noted that the “frequency of [the] c-met deletion may be underestimated because of cellular heterogeneity of tumour biopsy material.” Bièche, p. 142, col. 1, para. 2.

Thus, we find that the procedure described in Bièche differs from that required by claim 1 in only one significant aspect-- claim 1 requires that the abundance of the met DNA present in tumor breast tissue be compared with the abundance of met DNA present in normal tissue from the same breast.

As to the referenced difference, we agree with the examiner that the one of ordinary skill in the art at the time of the present invention would have found it obvious to compare the loss of heterozygosity at the c-met proto-oncogene with any normal cell or tissue type which expresses c-met, which would include normal breast tissue. The critical issue here being that Bièche demonstrates that it is the loss of heterozygosity in tumor DNA which is associated with poor prognosis. The only way to demonstrate said loss is by comparison with DNA from a normal cell or tissue which is known to express the c-met proto-oncogene.

The appellants argue that Bièche conclude that their studies show loss of heterozygosity on chromosome 7q and that the cause of the loss of DNA fragments is unknown. Brief, pp. 5-7. The appellants contend that since any portion or number of genes on chromosome 7 might have been lost along with the met gene, the teachings of Bièche do not suggest that the met gene itself was involved in breast cancer. Id., p. 7. The appellants rely on the declaration of Dr. Michael Dean (attached to the Brief as Exhibit B) for support. We find this argument and the declaration unpersuasive.

First, although Bièche frequently refers to the loss of heterozygosity or a deletion on chromosome 7q31, it is also stated in the publication that said loss reflects a

deletion of the met proto-oncogene. To that end, we direct attention to (i) “Fig. 1- Loss of heterozygosity at c-met proto-oncogene,” (ii) Table II “Multivariant Analysis of Metastasis-Free and Overall Survival in 121 Patients Heterozygous for c-met Proto-oncogene,” (iii) p. 141, col. 2, last sentence, which in a discussion of Table III states that the results “indicate[] that the c-met deletion is strongly predictive of metastasis in patients with grade III tumours,” and (iv) p. 142, col. 1, wherein it states that “Such loss of heterozygosity on chromosome 7q is consistent with cytogenetic findings in primary breast tumours, and the frequencies of the c-met deletion may be underestimated because of cellular heterogeneity of tumour biopsy material.”

Second, it was known in the art, and taught by Bièche, that the met gene located on chromosome 7q31 is a proto-oncogene. Bièche, p. 140, col. 1, para. 1; Park, the entire publication. The pmetH probe employed by Bièche was specific for the met proto-oncogene. Bièche, p. 139, col. 1, para. 1, p. 140, col. 1, para. 2. Thus, it is reasonable to conclude that the loss of heterozygosity from the region of chromosome 7 which was known to contain the met proto-oncogene would have suggested to those of ordinary skill in the art that the met proto-oncogene was responsible for the poor prognosis in the breast cancer patients reported by Bièche.

Third, although it is argued that any one of other genes present on chromosome 7 could be responsible for the initiation of breast malignancies, neither the appellants nor Dr. Dean state what “other genes” are present that could play a role in tumor

progression. Thus, while it may be true that some other gene, genes or gene fragments may be present on the 4.0 and 7.5 kb TaqI fragments we don't know what those other genes are. What we do know from Bièche's studies, however, is that the met proto-oncogene is present, and that breast cancer prognosis is decreased when one copy of the met proto-oncogene is lost. Thus, we conclude that the teachings of the Bièche would have suggested to those of ordinary skill in the art that the met proto-oncogene is involved in breast cancer.

As to the appellants' argument that Bièche did not suggest that one could predict cancer progression measuring the abundance of the met gene per se (Brief, p. 7), we direct attention to our discussion above wherein we point out that Bièche makes several references to the loss of heterozygosity as being a reflection of the loss of the met proto-oncogene. The loss of heterozygosity; i.e., the loss of one of two copies of the gene, manifestly reflects a decrease in the abundance of the met proto-oncogene in the breast tumor tissue.

The appellants argue that Bièche limited their study to DNA samples from patients having a heterozygous (LS) genotype for the TaqI restriction fragment length polymorphism (RFLP) on chromosome 7q31 and that identification of the specific gene involved in the genetic loss would be essential for the examination of patients having a homozygous (LL or SS) genotype. Brief, pp. 7-8. We find this argument unpersuasive. As pointed out by the examiner, claim 1 is not limited to patients having a homozygous

Appeal No. 1999-0339
Application 07/903,588

genotype, but rather it encompasses the heterozygous genotype described by Bièche. Accordingly, we find that this argument does not address a limitation present in the claim.

The appellants argue that Bièche's studies only indicate that one of the two parental copies of a region of chromosome 7 was deleted in breast tumors from patients having the LS genotype. Brief, p. 9. The appellants urge that this does not mean that there will be a difference between levels of met RNA and Met protein in normal and tumor tissues. We find this argument unpersuasive. We point out that claim 1 is not limited to a method of predicting the progress of breast cancer by comparing the abundance of met RNA and Met protein in normal and tumor breast tissue. The claim is also directed to a method wherein the abundance of met DNA in normal breast tissue is compared to the abundance of met DNA in tumor breast tissue. Accordingly, the appellants' argument does not address a limitation present in the claims.

In view of the foregoing, Rejection I is affirmed.

II.

The examiner argues that the appellants' method of predicting the progression of breast cancer using antibodies specific for the Met protein (claims 2-4) would have been obvious to one of ordinary skill in the art over the combined teachings of Bièche and Park.

As to the teachings of Bièche, we direct attention to our discussion above.

Appeal No. 1999-0339
Application 07/903,588

With respect to Park, we find that the publication discloses the nucleotide sequence of the met proto-oncogene cDNA and the deduced amino acid sequence of the Met protein. Park, p. 6381, Figure 2. In addition, Park discloses “Three MET-related proteins of 110, 140, and 160 kDa can be immunoprecipitated with a MET C-terminal anti-peptide antibody from human cell lines expressing the 9.0-kb MET RNA.” Id., p. 6379, col. 2, lines 1-3.

According to the examiner,

it would have been obvious to one of ordinary skill in the art at the time the invention was made to realize that the loss of the DNA locus of met would result in the loss of the associated Met gene product. Therefore, any gross correlations presented by Bièche et al. concerning met DNA would be readily extendable to immunomethods using the antibodies and methods of Park et al. [Answer, p. 8].

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). It is the examiner’s responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). This the examiner has not done.

Here, we find that the examiner’s conclusion of obviousness fails for two reasons.

First, the examiner's conclusion appears to be based on an incorrect supposition. That is, as we understand it, the examiner believes that DNA locus of met proto-oncogene has been lost, and therefore, he assumes that no Met protein will be present in the breast tumor cells. However, as pointed out by the appellants, this is not correct. Bièche's studies show that in breast tumor patients having the heterozygous (LS) genotype, only one of the two parental copies of the met proto-oncogene is lost in those patients whose prognosis is poor. Thus, one of ordinary skill in the art would have understood that some Met protein would still be present. Accordingly, we do not find any suggestion in Bièche to use the antibodies taught by Park to screen tumor tissue in order to predict the prognosis of breast cancer.

Second, the examiner has not pointed out any teaching or suggestion in Park to employ the antibodies described therein which recognize MET-related proteins in a method for predicting the prognosis of breast cancer which comprises comparing the binding of antibody specific for Met protein in normal breast tissue with the binding of said antibody in breast tumor tissue as described in claims 2-4.

On this record, the only place where we find any suggestion to employ antibodies in the manner required by the claims is in the specification. Thus, we find that he has engaged in impermissible hindsight in making his determination of obviousness. In re Gorman, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir.

Appeal No. 1999-0339
Application 07/903,588

1991)(“It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant’s structure as a template and selecting elements from references to fill the gaps”); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985); W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)(“To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher”).

Accordingly, Rejection II is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

JOAN ELLIS)
Administrative Patent Judge)
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Appeal No. 1999-0339
Application 07/903,588

DEMETRA J. MILLS
Administrative Patent Judge

ERIC GRIMES
Administrative Patent Judge

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Appeal No. 1999-0339
Application 07/903,588

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