

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 23

**UNITED STATES PATENT AND TRADEMARK OFFICE**

---

**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

---

Ex parte ANKE KLIPPEL, MICHAEL KAVANAUGH,  
STEPHEN HARRISON and LEWIS T. WILLIAMS

---

Appeal No. 2001-1378  
Application No. 08/832,571

---

ON BRIEF

---

Before ADAMS, MILLS and GRIMES, Administrative Patent Judges,

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-9, 15-16, 22-30 and 33-34 which are the claims on appeal in this application. Claims 31-32 are pending but are not before us on appeal. Brief, page 10.

Claim 1 is representative of the claims on appeal and reads as follows.

1. An isolated polynucleotide sequence comprising:
  - (a) a first nucleotide sequence comprising a sequence selected from the group consisting of:
    - (i) a nucleotide sequence encoding the p110 of PI 3-kinase protein and
    - (ii) a nucleotide sequence encoding a derivative or mutant of (a)(i) having single or multiple nucleotide substitutions, deletions or additions, said sequence encoding said derivative or mutant of (a)(i) having at least 50% identity to a native nucleotide sequence encoding p110, said derivative or mutant having 60-90% sequence identity to the native amino acid sequence of the p110 subunit of PI 3-kinase and an activity of the p110 subunit of PI 3-kinase protein; and
  - (b) a second nucleotide sequence comprising a sequence encoding a cell membrane targeting sequence, said second sequence being attached to the 5' or 3' end of said first sequence.

The references relied upon by the examiner are:

Hu et al. (Hu), "Ras-Dependent Induction of Cellular Responses by Constitutively Active Phosphatidylinositol-3 Kinase," Science, Vol. 268, pp 100-102 (1995)

Kapeller et al. (Kapellar), "Phosphatidylinositol 3-Kinase," BioEssays, Vol. 16, No. 8, pp. 565-576 (1994)

Varticovski et al. (Varticovski), "Activation of Phosphatidylinositol 3-Kinase in Cells expressing *abl* Oncogene Variants," Molecular and Cellular Biology, Vol. 11, No. 2, pp. 1107-1113 (1991)

Aronheim et al (Aronheim), "Membrane Targeting of the Nucleotide Exchange Factor Sos is Sufficient for Activating the Ras Signaling Pathway," Cell, Vol. 78, pp. 949-961 (1994)

Klippel et al. (Klippel 94), "The Interaction of Small Domains Between the Subunits of Phosphatidylinositol 3-Kinase Determines Enzyme Activity," Molecular and Cellular Biology, Vol. 14, No. 4, pp. 2675-2685 (1994)

Klippel et al. (Klippel 93), "A Region of the 85-Kilodalton (kDa) Subunit of Phosphatidylinositol 3-Kinase Binds the 110-kDa Catalytic Subunit In Vivo," Molecular and Cellular Biology, Vol. 13, No. 9, pp. 5560-5566 (1993)

Appeal No. 2001-1378  
Application No. 08/832,571

### Grounds of Rejection

Claims 1-9, 15-16, 22-30 and 33-34 stand rejected under 35 U.S.C. § 103(a) as obvious over Hu in view of Kapeller, Varticovski and Aronheim. We affirm this rejection.

Claims 1-9, 15-16, 22-30 and 33-34 stand rejected under 35 U.S.C. § 103(a) as obvious over Klippel 93 and 94 in view of Kapeller, Varticovski and Aronheim. We reverse this rejection.

### Grouping of Claims

According to appellants, there are two groupings of claims. Group 1 includes claims 1-9, 15-16, 22-30 and 33-34. Group II includes claims 31 and 32 which the examiner has indicated contain allowable subject matter. We decide this appeal on the basis of claim 1 as representative of claims 1-9, 15-16, 22-30 and 33-34.

### DISCUSSION

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, to the applied prior art references, and to the respective positions articulated by the appellants and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellants regarding the above-noted rejection, we make reference to the

Appeal No. 2001-1378  
Application No. 08/832,571

Examiner's Answer for the examiner's complete reasoning in support of the rejection, and to the appellants' Brief for the appellants' arguments thereagainst. As a consequence of our review, we make the determinations which follow.

### Claim Interpretation

Our appellate reviewing court stated in Pandit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1567-1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), cert denied, 481 U.S. 1052 (1987):

Analysis begins with a key legal question -- what is the invention claimed? Courts are required to view the claimed invention as a whole. 35 U.S.C. 103. Claim interpretation, in light of the specification, claim language, other claims and prosecution history, is a matter of law and will normally control the remainder of the decisional process. [Footnote omitted.]

To that end, we also note that during ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

Claim 1 is directed to an isolated polynucleotide sequence comprising:

(a) a first nucleotide sequence comprising a sequence selected from the group consisting of:

(i) a nucleotide sequence encoding the p110 of PI 3-kinase protein and

Appeal No. 2001-1378  
Application No. 08/832,571

(ii) a nucleotide sequence encoding a derivative or mutant of (a)(i) having single or multiple nucleotide substitutions, deletions or additions, said sequence encoding said derivative or mutant of (a)(i) having at least 50% identity to a native nucleotide sequence encoding p110, said derivative or mutant having 60-90% sequence identity to the native amino acid sequence of the p110 subunit of PI 3-kinase and an activity of the p110 subunit of PI 3-kinase protein; and

(b) a second nucleotide sequence comprising a sequence encoding a cell membrane targeting sequence, said second sequence being attached to the 5' or 3' end of said first sequence.

In interpreting claim 1, we note the open ended claim language “comprising” both in the preamble of the claim and in the description of the first nucleotide sequence leaves the polynucleotide sequence (fusion protein) open to the inclusion of additional components. The term “comprising” is inclusive and does not exclude additional, unrecited elements or method steps. Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986), cert. denied, 479 U.S. 1030 (1987).

35 U.S.C. § 103

Claims 1-9, 15-16, 22-30 and 33-34 stand rejected under 35 U.S.C. § 103(a) as obvious over Hu in view of Kapeller, Varticovski and Aronheim.

Appeal No. 2001-1378  
Application No. 08/832,571

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). An obviousness analysis requires that the prior art both suggest the claimed subject matter and reveals a reasonable expectation of success to one reasonably skilled in the art. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

It is the examiner's position that (Answer, page 3-4):

Hu et al. disclose the p110\* construct, which comprises DNA encoding the p110 subunit of PI 3-kinase and the iSH2 portion of the p85 subunit, attached via a "glycine kinker [sic]" (See Fig. 1, page 100). In the disclosed p110\* construct, the nucleotide sequences encoding the Myc-tagged p110 subunit and the iSH2 portion of the p85 subunit having a "glycine kinker [sic]" at the COOH terminus also represent nucleotide sequences encoding for a derivative or mutant of the wild type p110 subunit and a portion of the wild type p85 subunit, respectively, as encompassed in certain embodiments of the instantly claimed invention... The p110\* DNA construct and various derivatives thereof were transiently transfected and expressed in COS-7 cells.... Immunoprecipitates of transfected cells' lysates containing the enzyme were analyzed for the expression level and for the PI-3 kinase activity via the production of [<sup>32</sup>P] PI-3 phosphate (PIP). The encoded p110\* protein is found to be a constitutively active form of PI 3-kinase. ...

Hu et al. do not teach a construct further comprising DNA encoding a membrane targeting sequence. However, Kapeller et al. teach that localization of PI 3-kinase to the plasma membrane is expected to increase the 3-kinase activity, since it brings the enzyme into closer contact with its substrates... Varticovski et al. also teach that PI 3-kinase

must be localized to a membrane to work efficiently.... Aronheim et al. teach methods for localizing proteins to membranes by addition of myristoylation, farnesylation and palmitoylation signal sequences....

The examiner summarizes (Answer, pages 4-5):

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the p110\* construct of Hu et al. by adding DNA encoding membrane localization sequences as taught by Aronheim et al. Kapeller et al. and Varticovski et al. provide both motivation to make this modification and a reasonable expectation of success, in that they each indicate that one of ordinary skill in the art expected that PI 3-kinase activity would be increased by targeting the enzyme to membranes, where the enzyme substrates are located. Even for a constitutively active p110\* mutant, one of ordinary skill in the art would still be motivated to localize it to the cell membranes where its substrates are, such that optimal production of its phosphorylated lipid products and maximal physiological responses mediated by these lipid products could be obtained.

We agree that the examiner has presented sufficient evidence to support a prima facie case of obviousness. In particular, Hu describes a constitutively active PI 3-kinase linked to the iSH2 portion of the p85 subunit. Kapellar indicates that PtdIns-3-kinase substrate is localized at the plasma membrane. Kapeller, page 571, col. 1. Varticovski suggests that amino terminal myristoylation is needed to place an abl protein/PI 3 kinase complex at a membrane location where lipid phosphorylation can occur efficiently. Varticovski, page 1112, col. 1. Similarly, Aronheim generally describes the binding "of growth factors to cell surface receptors results in receptor dimerization and activation of their intrinsic tyrosine kinase, leading to intermole-

cular autophosphorylation.” Aronheim, page 949, col. 1. Aronheim states that myristoylation, palmitoylation and farnesylation signals are sufficient for membrane targeting of heterologous proteins. Id.

In our view, the cited references would have provided the requisite reason, suggestion or motivation to one of ordinary skill in the art to add the myristoylation, palmitoylation and farnesylation signals taught by Aronheim to target the constitutively active P110 of Hu to the membrane region, closer to its substrate with a reasonable expectation of success in view of Kapellar and Varticovski.

Where the prior art, as here, gives reason or motivation to make the claimed invention, the burden then falls on an appellants to rebut that prima facie case. Such rebuttal or argument can consist of any other argument or presentation of evidence that is pertinent. In re Dillon, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991).

Appellants argue that Hu teaches away from the invention as claimed as Hu teaches that “the only way to activate wild-type PI 3-kinase, is the result of a combination of binding, phosphorylating and localizing of wild-type PI 3-kinase by tyrosine kinases.” Brief, page 13. According to Appellants, this teaches away from adding membrane targeting lipid moieties to a wild-type PI 3-kinase or to Hu's PI 3-kinase polynucleotide fusion protein construct.

We disagree. In particular, and notwithstanding appellants' arguments with respect to wild-type PI 3-kinase, Hu describes a constitutively active PI 3 kinase fusion protein. Arguments relating to activation of PI 3-kinase, are not relevant to the constitutively active form of PI 3-kinase disclosed by Hu. This is also true with respect to appellants' teaching away arguments proposed for Kapeller, Varticovski and Aronheim. Appellants argue that these references teach that "other functional domains of p85, which are not components of the claimed polynucleotide fusion constructs (nor encoded by them), may be important for protein-protein interactions and required for PI 3-kinase activity." Brief, page 14. Appellants argue that Aronheim teaches that localization to the plasma membrane alone may not be sufficient to produce catalytically active PI 3-kinase. Brief, page 15. We find such arguments are not relevant to the PI 3-kinase fusion protein disclosed by Hu which is already constitutively active.

Appellants argue there is no motivation to combine the cited art and that the examiner applies an "obvious to try" argument which is not the appropriate legal standard. Brief, page 17. Appellants argue that the cited references "fail to teach or suggest that the addition of membrane localization signals to a constitutively active PI 3-kinase fusion construct would enhance the properties of that construct." Id. As discussed herein, we find the cited references would have provided the requisite suggestion and likelihood of success on the part of one of ordinary skill in the art, that the localization of PI 3-kinase to the plasma membrane would have resulted in an

Appeal No. 2001-1378  
Application No. 08/832,571

expected increase in PI 3-kinase activity, since it brings the enzyme into closer contact with its substrates.

Appellants have failed to provide sufficient argument and/or evidence to rebut the examiner's prima facie case of obviousness. On balance, we believe that the totality of the evidence and argument presented by the examiner and appellants weighs in favor of finding the claimed invention obvious in view of the cited references. The rejection of the claims for obviousness of the claimed invention over Hu in view of Kapeller, Varticovski and Aronheim is affirmed.

35 U.S.C. § 103(a)

Claims 1-9, 15-16, 22-30 and 33-34 stand rejected under 35 U.S.C. § 103(a) as obvious over Klippel 93 and 94 in view of Kapeller, Varticovski and Aronheim.

Klippel 94 is relied on by the examiner for the disclosure of separate constructs encoding the p110 and p85 subunits of PI 3-kinase, as well as p85 subunit fragments containing the iSH2 domain. Klippel 94 shows that p110, in combination with either p85 or its fragments containing the iSH2 domain, has PI 3-kinase activity in vivo. Klippel 94, page 2682, col. 1, Answer, page 5. Klippel 94 also teaches cells expressing said constructs and a method for making 3' phosphorylated PI lipid by incubating the enzyme with substrate. Answer, pages 5-6. The examiner acknowledges that Klippel does not teach constructs comprising DNA encoding a membrane targeting sequence

or a combination of both coding sequences (p110 and p85) on the same construct. Answer, page 6, Paper No. 9, page 6, Brief, page 18. For reasons similar to those indicated above, the examiner cites Kapeller, Varticovski and Aronheim as evidence of knowledge in the art that localization of PI 3-kinase to the plasma membrane is expected to increase the PI 3-kinase activity, since it brings the enzyme into closer contact with its substrates, and methods for localizing proteins to membranes by addition of myristoylation, farnesylation and palmitoylation signal sequences.

. Appellants argue that the examiner has failed to set forth a prima facie case of obviousness. Brief, page 22. Appellants argue that (Brief, page 19):

At the time of the invention, one of ordinary skill in the art would not equate the *in vivo* coexpression of PI 3-kinase subunits, which assumes conformation that allows them to specifically bind to one another, with that which occurs “when two subunits are coexpressed [end to end] as a fusion protein.”

We agree with the appellants that the cited art fails to provide the requisite expectation of success to establish a prima facie case of obviousness. According to appellants, Klippel 94 teach that association in vitro of the two subunits produced separately did not produce an active enzyme, teaching away from an expectation that the claimed fusion construct would produce active enzyme. Id. In addition, Klippel 93 teach that “a change in the phosphorylation state of the [p110 and p85] subunits [of PI 3-kinase] after association with activated receptor molecules may induce conformational change and thereby modulate PI 3-kinase activity.” Id. Furthermore, appellants argue

that Kapeller, Varticovski and Aronheim teach that “other functional domains of p85, which are not components of the claimed polynucleotide fusion constructs (nor encoded by them), may be important for protein-protein interactions and required for PI 3-kinase activity *e.g.*, SH2 and SH3 domains.” Brief, page 14. Appellants argue that Aronheim teaches that localization to the plasma membrane alone may not be sufficient to produce catalytically active PI 3-kinase. We find such arguments regarding the PI 3-kinase constructs disclosed by Klippel 93 and 94, which are not fusion constructs and which, when combined *in vitro*, fail to show PI 3-kinase activity, to be relevant with regard to the expectation of success of one of ordinary skill in the art at the time of the present invention. In our view, the cited references, as a whole, support appellants' argument that one of ordinary skill in the art at the time of the invention would perceive that possibly other DNA sequences or conformational changes are necessary to provide for an active PI 3-kinase.

The examiner responds, arguing that the problem of inactivity which occurs when the two subunits produced separately is “overcome when the two subunits are coexpressed and allowed to associate *in vivo*. This is precisely what occurs when the two subunits are co-expressed as a fusion protein *in vivo*, and at the time the invention was made the art of making a fusion protein with the desired activity is routine for one of ordinary skill in the art.” Answer, page 10.

Appeal No. 2001-1378  
Application No. 08/832,571

We disagree. The examiner has failed to provide evidence to support the statement that expressing the two subunits as a fusion protein in vivo overcomes the problem of inactivity which occurs when the two units are produced separately. We note that the examiner does not rely on Hu, as a basis for this rejection.

After evidence or argument is submitted by the applicant in response to an obviousness rejection, "patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of the argument." In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); see In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787 (Fed. Cir. 1984) ("All evidence on the question of obviousness must be considered, both that supporting and that rebutting the prima facie case."). On balance, we believe that the totality of the evidence presented by the examiner and appellants weighs in favor of finding the claimed invention nonobvious over Klippel 93 and 94 in view of Kapeller, Varticovski and Aronheim. The rejection is reversed.

#### CONCLUSION

The rejection of claims 1-9, 15-16, 22-30 and 33-34 under 35 U.S.C. § 103(a) as obvious over Hu in view of Kapeller, Varticovski and Aronheim is affirmed. The rejection of claims 1-9, 15-16, 22-30 and 33-34 under 35 U.S.C. § 103(a) as obvious over Klippel 93 and 94 in view of Kapeller, Varticovski and Aronheim is reversed.

Appeal No. 2001-1378  
Application No. 08/832,571

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

AFFIRMED

DONALD E. ADAMS	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
DEMETRA J. MILLS	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
	)	
ERIC GRIMES	)	
Administrative Patent Judge	)	

DJM/dym

Appeal No. 2001-1378  
Application No. 08/832,571

Chiron Corporation  
Intellectual Property - R440  
P.O. Box 8097  
Emeryville CA 94662-8097