

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 44

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte STEFANO MARULLO,
COLETTE DELAVIER,
LAURENT EMORINE, and
DONNY STROSBURG

Appeal No. 2001-1436
Application No. 08/422,612

ON BRIEF

Before WILLIAM F. SMITH, MILLS, and GRIMES, Administrative Patent Judges.
GRIMES, 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 16-25, 41, and 44-53, all of the claims remaining. Claim 41 is representative and reads as follows:

41. A yeast cell stably transformed with an expression vector comprising:
 - (a) an insert encoding a mammalian receptor comprising seven hydrophobic transmembrane segments, extracellular and intracellular loops, an extracellular amino terminal region, and a carboxyl terminal cytoplasmic region; and

- (b) a control region capable of being recognized by polymerases of the yeast cell for expression of said polypeptide in said yeast cell; and

wherein, after expression, said polypeptide is incorporated into a cell membrane of said yeast cell and said polypeptide is capable of binding a ligand of said mammalian receptor.

The examiner relies on the following references:

Dull et al. (Dull)	4,859,609	Aug. 22, 1989
King et al. (King)	5,482,835	Jan. 09, 1996

Dohlman et al. (Dohlman), "A Family of Receptors Coupled to Guanine Nucleotide Regulatory Proteins," Biochemistry, Vol. 26, No. 10, pp. 2657-2664 (1987)

Lübbert et al. (Lübbert), "cDNA cloning of a serotonin 5-HT_{1C} receptor by electrophysiological assays of mRNA-injected Xenopus oocytes," Proc. Natl. Acad. Sci. USA, Vol. 84, pp. 4332-4336 (1987)

Dietzel et al. (Dietzel), "The Yeast SCG1 Gene: A G α -like Protein Implicated in the a- and α -Factor Response Pathway," Cell, Vol. 50, pp. 1001-1010 (1987)

Kobilka et al. (Kobilka), "Cloning, Sequencing, and Expression of the Gene Coding for the Human Platelet α_2 -Adrenergic Receptor," Science, Vol. 238, pp. 650-656 (1987)

Claims 16-25, 41, and 44-53 stand rejected under 35 U.S.C. § 112, first paragraph, as nonenabled.

Claims 16-25, 41, 44-9, 51, and 52 stand rejected under 35 U.S.C.

§ 102(e) as anticipated by King.

Claim 50 stands rejected under 35 U.S.C. § 103 as obvious over King.

Claims 16-25, 41, and 44-53 stand rejected under 35 U.S.C. § 103 as obvious over Dull, Koblika, Dohlman, Dietzel, and Lübbert.

We reverse.

Background

The specification discloses expression of mammalian G protein-coupled receptors in single-celled hosts such as bacteria or yeast. “G proteins are proteins having the capacity to interpose themselves structurally and functionally between receptors and enzymes catalyzing the production of intracellular mediators (such as adenylate cyclase . . .).” Specification, page 1. “These [G] proteins have transduction and coupling functions and are characterized by a monomeric structure composed of three protein subunits[:] alpha, beta, gamma.” Id.

The G protein-coupled receptors “include regions exposed at the surface of the host cells which have specific affinities for a large variety of ligands.” Id., pages 1-2. “A preferred family of receptors . . . comprises β 1, β 2, α 1, and α 2-adrenergic receptors, muscarinic receptors belonging to the subtypes M1 to M4 and the receptor for the neuropeptide known as ‘substance K’. These receptors appear to possess a common structural organization within the plasma membrane, usually characterized by seven hydrophobic transmembrane segments between which are inserted extra- and intra-cellular loops, by an extracellular amino-terminal region and by a cytoplasmic carboxyl-terminal region.” Id., page 2 (reference numerals omitted).

The specification discloses that when genes encoding a mammalian membrane receptor are expressed in unicellular hosts “under the control of a promoter recognized by the polymerases of [the] unicellular host,” the expressed product is transported into the membranes of the host cell and is configured such that the receptor proteins can be bound by the appropriate ligands. See id., page 3. The specification also discloses that the preferred host cell is E. coli, but other unicellular organisms can also be used. Other specifically disclosed systems are S. cerevisiae host cells carrying a 2 μ or PBM 258 plasmid and expressing the mammalian gene under the control of the alcohol dehydrogenase I or galactokinase promoter. See page 4.

The specification discloses that unicellular hosts expressing mammalian membrane receptors are useful for “study[ing] the affinity of various types of molecules for a specific membrane receptor.” Page 7. See also page 10:

The present invention also relates to a procedure for the detection of the capacity of a molecule to behave as a ligand for a membrane receptor, this process comprising:

- a/ the placing in contact of the molecule with a unicellular organism previously transformed by a vector, itself modified by an insert coding for this membrane receptor, . . . [and]
- b/ the detection of the possible formation of a complex of the ligand-receptor type.

Discussion

At the outset, we commend both the examiner and Appellants' counsel for their efforts in briefing this case. The Examiner's Answer and Appellants' briefs explain the technically complex subject matter clearly and thoroughly, and it is clear that both sides put a lot of time and effort into making their case. On balance, however, we conclude that the examiner's rejections cannot be sustained on this record.

Claim 41, the broadest claim on appeal, is directed to a yeast cell transformed with an expression vector encoding a mammalian G protein-coupled receptor and a control region (e.g., promoter) that is functional in the yeast cell. Claim 41 also requires that "after expression, [the receptor] is incorporated into a cell membrane of said yeast cell and [the receptor] is capable of binding a ligand of said mammalian receptor."

The examiner rejected various claims as nonenabled and as anticipated or obvious in view of King. These rejections, however, are all related to the rejection of all the claims (including claim 41) as obvious in view of the combined disclosures of Dull, Kobilka, Dohlman, Lübbert, and Dietzel. We will begin our analysis with this rejection.

The examiner cited Dull as showing "production of an expression vector encoding a receptor protein and the employment of that expression vector to obtain the expression of that protein in a yeast host cell to permit the identification of compounds which can act as agonists and antagonists to that receptor." Examiner's Answer, page 7. The examiner acknowledged that Dull

does not exactly disclose the claimed yeast cells because Dull teaches “expression of chimeric receptors having a single extracellular domain, a single transmembrane domain and a single cytoplasmic domain whereas the instant claims require a vector encoding a G protein-coupled receptor.” Id., page 8.

The examiner cited Kobilka, Dohlman, and Lübbert as “show[ing] that isolated DNAs encoding the G protein-coupled receptors of the instant invention were known and used in the art prior to the filing of the instant application.” Id. Finally, he cited Dietzel as providing “three critical elements” that supported a reasonable expectation of success. The examiner cited Dietzel as showing (1) that yeast pheromone receptors are very similar to mammalian G protein-coupled receptors, (2) that expression of mammalian proteins in yeast cells was routine in the art at the time the instant application was filed, and (3) that a rat G α subunit functionally interacted with “the endogenous mating factor receptor of the host cell as well as the S. cerevisiae G β and G γ subunits and/or downstream effectors.” Examiner’s Answer, pages 8-9.

The examiner concluded that

[g]iven the well known ease with which S. cerevisiae is propagated and genetically manipulated relative to mammalian cells, as demonstrated by Dietzel et al., an artisan would have found it prima facie obvious to have incorporated an expression vector encoding a mammalian G protein-coupled receptor such as any one of those that were described in the Kobilka et al., Dohlman et al. and Lübbert et al. publications into S. cerevisiae to permit the identification of agonists and antagonists thereto as taught [by] Dull et al. in the absence of other mammalian receptors. That artisan had more than a reasonable expectation that a mammalian G

protein-coupled receptor could be functionally expressed in S. cerevisiae because S. cerevisiae was already known to naturally produce G proteins and G protein-coupled receptors and because the functional expression of other mammalian receptor proteins in S. cerevisiae was a routine practice in the art at the time of the instant invention.

Examiner's Answer, page 10.

Appellants argue that the cited references do not provide adequate motivation to combine their respective teachings in such a way as to yield the claimed invention. See the Appeal Brief, page 39.¹ Appellants focus on Dietzel, and thoroughly review Dietzel's data and conclusions. See the Appeal Brief, pages 47-56. Based on this review, Appellants argue that Dietzel leads away from the claimed invention, because it suggests that a mammalian G protein-coupled receptor would not be fully functional if expressed in yeast. Appeal Brief, page 56. See also the Reply Brief, pages 3-7.

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art,

¹ Appellants state that, during prosecution, they "repeatedly asserted that the cited documents do not provide a reasonable expectation of success." Appeal Brief, page 39. However, Appellants chose not to "reiterate those points in th[e] brief." Id. Therefore, we consider this argument to have been waived for purposes of the appeal. See 37 CFR § 1.192(a) ("The brief . . . must set forth the authorities and arguments on which appellant will rely to maintain the appeal.").

not in the applicant's disclosure." In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) (citations omitted).

As we have noted, the examiner did a commendable job in this case. We nonetheless conclude that the § 103 rejection is not supported by a preponderance of the evidence in the record. We are persuaded, specifically, by Appellants' argument based on the Dietzel reference. See the Appeal Brief, pages 46-57 and the Reply Brief, pages 3-7. We agree with Appellants that Dietzel would have led those skilled in the art to expect that a mammalian G protein-coupled receptor would not be functional in Dull's assay method if expressed in a yeast cell.

The exhibit attached to the Examiner's Answer shows how the G protein system generates an intracellular signal in response to an extracellular ligand. The G protein consists of three subunits (α , β , and γ). In the resting state, the α subunit associates with the other subunits and with a molecule of GDP. The system also includes two other proteins (a receptor and an effector).

Signal transduction is turned on when the receptor binds its ligand. Ligand binding causes the receptor to interact with the G protein's α subunit and cause it to exchange its GDP for GTP. This in turn causes the α subunit to dissociate from the β and γ subunits, and bind to the effector protein. The effector protein is activated and the appropriate signal is generated, until the α

subunit converts the bound GTP back to GDP, and reassociates with the β and γ subunits, resetting the system to its resting state.

Thus, the extracellular signal (the receptor binding its ligand) is transduced into an intracellular signal (effector protein activity) through the interaction of the receptor with the G protein α subunit. The skilled artisan would therefore expect that if the receptor could not interact with the G protein α subunit, the G protein would not dissociate, and no signal would be produced, in response to the ligand/receptor binding. The disclosure of the Dietzel reference must be considered in light of this expectation.

Dietzel isolated a yeast gene encoding a protein involved in the mating factor (pheromone) response pathway. Dietzel concluded, based on sequence homology and structural features, that the protein was a homolog of a G protein α subunit and named the gene SCG1, for *Saccharomyces cerevisiae* G protein gene. See page 1001. Dietzel also showed that yeast strains having mutations in the SCG1 gene could be partially complemented by a mammalian (rat) gene encoding a G protein α subunit. See pages 1005-1006.

The examiner relies on this complementation to provide an expectation of success. See the Examiner's Answer, pages 9-10:

Since this partial complement would require the rat $G\alpha$ subunit to functionally interact (couple) with the endogenous mating factor receptor of the host cell as well as the *S. cerevisiae* $G\beta$ and $G\gamma$ subunits and/or downstream effectors as illustrated in Figure 6 therein, then this reference shows that the *S. cerevisiae* mating factor receptors are, by definition, G protein-coupled receptors since they transduce their ligand activated signals directly through G proteins. . . . Th[e] artisan had more than a reasonable expectation that a mammalian G protein-coupled receptor could be

functionally expressed in S. cerevisiae because S. cerevisiae was already known to naturally produce G proteins and G protein-coupled receptors and the functional expression of other mammalian receptor proteins in S. cerevisiae was a routine practice in the art at the time of the instant invention.

Appellants, however, point out the lack of support for the examiner's position that "this partial complement would require the rat G α subunit to functionally interact (couple) with the endogenous mating factor receptor of the host cell." Specifically, Appellants point to Dietzel's discussion of their experimental data. See the Appeal Brief, pages 52-57. Dietzel concludes that their data can be explained by either of two models, shown in Figure 6. In both of the models, the rat G protein α subunit does not interact with the yeast receptor protein. See page 1007, right-hand column (emphasis added):

Both models are consistent with the phenotypes associated with SCG1 and with the ability of rat α_s [α subunit] to complement an scg1 mutation.

. . . The mating defect of the scg1 mutants expressing rat α_s suggests that this heterologous protein is not able to interact with activated a- or α -factor receptor; therefore, GDP-GTP exchange would not occur in either model, resulting in an inability to activate the pheromone response pathway.

We agree with Appellants that Dietzel's conclusion would have led those of skill in the art to doubt the success of combining a mammalian G protein-coupled receptor gene with Dull's yeast assay system. Specifically, Dietzel's conclusion that a mammalian G protein α subunit did not interact with the yeast receptor would lead those skilled in the art to reasonably expect that the yeast G protein α subunit would also not interact with a mammalian receptor. Therefore, those skilled in the art would expect that a mammalian G protein-coupled

receptor, when expressed in yeast cells, would not function to cause dissociation of the yeast G protein or transduce a signal into the yeast cell.

Dull's system relies on transduction of a signal by the heterologous receptor, in order to assay for ligand binding. See column 3, lines 9-13: "The hybrid receptor of this invention is useful in screening methods for identifying receptor-active agonistic drugs. One incubates the hybrid receptor with the candidate drug and assays for the generation of a signal by the heterologous reporter polypeptide." The assayable signal can be the activity of an enzymatic effector protein (column 3, lines 13-16) or activation of G protein by the receptor (column 11, lines 21-28). In any case, however, Dull's method depends on generation of an intracellular signal in response to ligand binding by the heterologous receptor.

This requirement for functional signal transduction would have led those skilled in the art to expect that a mammalian G protein-coupled receptor, expressed in yeast, could not be used in Dull's assay method. Dietzel teaches that mammalian G protein α subunit does not interact with a yeast receptor, which would have led those skilled in the art to also expect the converse: that a yeast G protein α subunit would not interact with a mammalian receptor. Since the mammalian receptor would not be expected to interact with the yeast G protein, those skilled in the art would have expected that a mammalian G protein-coupled receptor would not produce a signal, even induction of G protein dissociation, if expressed in yeast cells. Therefore, those skilled in the art would

not have expected an intact, mammalian G protein-coupled receptor gene to be useful in Dull's method, and would not have been motivated to combine the two.

"It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements." Arkie Lures Inc. v. Gene Larew Tackle Inc., 119 F.3d 953, 957-58, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997). The references cited by the examiner clearly show that genes encoding mammalian G protein-coupled receptors were known in the art, as was expression of heterologous genes in yeast cells. However, "all of the relevant teachings of the cited references must be considered in determining what they fairly teach to one having ordinary skill in the art. The relevant portions of a reference include not only those teachings which would suggest particular aspects of an invention to one having ordinary skill in the art, but also those teachings which would lead such a person away from the claimed invention." In re Mercier, 515 F.2d 1161, 1165-66, 185 USPQ 774, 778 (CCPA 1975) (emphasis in original, citations omitted). We agree with Appellants that when the cited references are considered in their entirety, they would not have suggested the claimed invention to those of skill in the art. The rejection is therefore reversed.

As noted above, the other rejections in the Examiner's Answer are related to the obviousness rejection discussed above. Specifically, the examiner rejected all of the claims as nonenabled,

based solely on Appellant's [sic] extensive arguments that the prior art of record did not provide an artisan with a reasonable expectation that a mammalian G protein-coupled receptor could be

expressed in S. cerevisiae in combination with the Examiner's position that an artisan would not have expected the su[rp]rising and unexpected results obtained by Appellant[s] in E. coli to be predictive of prophetic results in the completely unrelated organism S. cerevisiae.

Examiner's Answer, pages 2-3 (emphasis in original).

We understand the examiner's position to be based on Appellants' arguments, presented earlier in prosecution but not repeated in the Appeal Brief, that the prior art would not have provided a reasonable expectation of success. As we understand it, the examiner's reasoning is that the claims must be either obvious or nonenabled: if Appellants are correct that the claims are nonobvious (due to lack of expectation of success), then they are nonenabled because the specification provides no guidance to supply the expectation allegedly missing from the prior art.

We do not agree that our reversal of the obviousness rejection mandates affirmance of the nonenablement rejection. The examiner's obviousness rejection is based on substituting DNA encoding an intact mammalian G protein-coupled receptor into Dull's assay system. Dull's system relies on functional transduction of a signal by the heterologous receptor to generate a positive response in the assay. Thus, to be used in Dull's system, a mammalian G protein-coupled receptor would have to generate a signal – either dissociation of the G protein or activation of the effector protein – in response to binding a ligand. In view of Dietzel's disclosure, however, a skilled artisan would not have expected functional signal transduction by a mammalian G protein-coupled receptor expressed in yeast cells.

The instant claims, by contrast, do not require transduction of a signal by the receptor; all the claims require is that the receptor bind its ligand. Thus, the instant claims do not depend on interaction between the mammalian G protein-coupled receptor and the yeast G protein α subunit. In the examples disclosed in specification, binding of ligand to receptor is measured directly, using a labeled ligand. See, e.g., pages 16-17 and 23-24. Thus, the specification discloses a method of assaying for ligand-binding by the heterologous receptor, even if the receptor does not transduce a signal. The examiner has not shown that undue experimentation would have been required to use yeast cells expressing a mammalian G protein-coupled receptor in the disclosed assay method. The rejection for nonenablement is reversed.

As recognized by the examiner, our reversal of the nonenablement rejection mandates reversal of the rejections based on King. See the Examiner's Answer, page 3:

The pending rejection for anticipation and obviousness under 35 U.S.C. § 102(e) based upon the King et al. patent is not a separate issue because it is based solely upon the enablement rejection of record. If the instant application is not enabled for the now claimed invention then it can not [sic], by law, receive benefit under 35 U.S.C. § 120 from any prior application and, therefore, any intervening art must be applied where appropriate. If the enablement rejection is withdrawn [sic, reversed] then the rejection for anticipation and obviousness based upon the intervening King et al. reference must also be withdrawn [sic, reversed].

The rejections over King are reversed.

Summary

We reverse the rejection based on Dull, Dietzel, et al., because the cited references would not have motivated a person skilled in the art to combine their respective teachings. We reverse the rejection for nonenablement because the examiner has not shown that making or using the claimed invention would have required undue experimentation, and we reverse the rejections based on King because King is not available as prior art.

REVERSED

WILLIAM F. SMITH)	
Administrative Patent Judge)	
)	
)	
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