The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board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. 21

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RAJENDER KAMBOJ, CANDACE E. ELLIOTT,
and STEPHEN L. NUTT;

Ex parte ROBERT L. FOLDES and RAJENDER KAMBOJ;

Ex parte ROBERT L. FOLDES, SALLY-LIN ADAMS, and RAJENDER KAMBOJ;

and

Ex Parte ROBERT FOLDES, ROBERT FANTASKE, SALLY-LIN ADAMS,
and RAJENDER KAMBOJ

Consolidated Appeals[1]

ON BRIEF

Before, WILLIAM F. SMITH, ADAMS, and MILLS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

[1] See Appendix A, attached hereto, for a listing of Appeal and Application Numbers (Nos.)

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BACKGROUND

This decision consolidates the fourteen appeals listed in Appendix A. Each appeal relates to one of three classes of glutamate receptors. Glutamate receptors are the predominant excitatory neurotransmitter receptor in the mammalian brain and are activated in a variety of normal neurophysiological processes.[2] Four major classes of glutamate receptors are well characterized: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate, and 2-amino-4-phosphonobutanoate.[3]

The applications on appeal involve the kainate, AMPA, and NMDA receptor classes. As illustrated in Appendix B, the appeals not only fall within one of three receptor classes, but are further divided into subclasses, with respect to the kainate, and AMPA receptor classes.

While four different examiners were involved in this series of appeals, a single reference, Puckett[4], provides a common thread which relates all of the appeals. All but two[5] of the appeals, contain at least one rejection under 35 U.S.C. § 103 upon which Puckett is relied upon in some manner. Additionally, the two appeals that do not expressly rely on Puckett in the statement of the rejection, make reference to Puckett in the body of the examiner's Answer.

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[2] Puckett et al. (Puckett), "Molecular cloning and chromosomal localization of one of the human glutamate receptor genes," Proc. Natl. Acad. Sci., USA, Vol. 88, pp. 7557-561 (1991).
[3] Sun et al. (Sun), "Molecular cloning, chromosomal mapping, and functional expression of human brain glutamate receptors," Neurobiology, Vol. 89, pp. 1443-447 (1992).
[4] Supra, n.2.

However, we find that the examiners handling this series of applications differ, inter alia, in their interpretation of the Puckett reference.

While the issues, references cited and reasoning for the rejections are quite similar in each of the appeals, it also appears that events have overtaken a number of appeals. As illustrated in Appendix B a number United States Patents have issued with claims that appear to conflict with the continued rejection of some of the claims on appeal, and/or with the reasoning upon which the examiners use to reject the claims on appeal.

Therefore, in the interest of administrative economy, and to avoid further delay in the prosecution of these applications, we have consolidated these appeals into one decision.

DECISION ON APPEAL

This is a decision on the appeals listed in Appendix A under 35 U.S.C. § 134 from the examiners' rejections in each of the applications. This opinion is divided into three sections based on the receptor class (kainate, AMPA, or NMDA) to which the appeal relates. Two sections (kainate and AMPA) are further divided to address appeals relating to the receptor subclasses (e.g. EAA4, EAA5, GLUR1, GLUR2, etc.). Within each section, the corresponding appeals will be discussed in order of appeal number, and claims that illustrate the subject matter of each appeal will be presented, along with the grounds of rejection made therein.

In reaching our decision in these appeals, we have given careful consideration to the appellants' specification and claims, and to the respective positions articulated by the appellants and the examiner. We will make reference to

[5] Appeal Nos. 2000-1779 and 2000-1780.

the examiner's Answers, and Supplemental Answers (when presented) for the examiner's reasoning in support of the rejections. We will further reference appellants' Briefs and Reply Briefs (when presented) for appellants' arguments in favor of patentability.

REFERENCES

The references relied upon by the examiners are presented below with a footnote corresponding to the appeal upon which they relate:

Bettler et al. (Bettler '90), "Cloning of a Novel Glutamate Receptor Subunit, GluR5: Expression in the Nervous System during Development," Neuron, Vol. 5, pp. 583-95 (1990)[6]

Bettler et al. (Bettler '92), "Cloning of a Putative Glutamate Receptor: A Low Affinity Kainate-Binding Subunit," Neuron, Vol. 8, 257-65 (1992)[7]

Birnbaumer et al. (Birnbaumer), "Development and Characterization of a Mouse Cell Line Expressing the Human V2 Vasopressin Receptor Gene," Mol. Endocrinol., Vol. 4(2), pp. 245-54 (1990)[8]

Blackstone et al., (Blackstone), "Immunological Detection of Glutamate Receptor Subtypes in Human Central Nervous System," Annals of Neurology, Vol. 31(6), pp. 680-83 (1992)[9]

Cutting et al. (Cutting), "Cloning of the γ-aminobutyric acid (GABA) ρ_1 cDNA: A GABA receptor subunit highly expressed in the retina," Proc. Natl. Acad. Sci., USA, Vol. 88, pp. 2673-677 (1991)[10]

Durand et al. (Durand), "Splice variants of the N-methyl-D-aspartate receptor NR1 identify domains involved in regulation by polyamines and protein kinase C," Proc. Natl. Acad. Sci., USA, Vol. 90, pp. 6731-735 (1993)[11]

Egebjerg et al. (Egebjerg), "Cloning of a cDNA for a glutamate receptor subunit activated by kainate but not AMPA," Nature, Vol. 351, pp. 745-48 (1991)[12]

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[6] (Bettler '90) Appeal No.: 1999-0350.
[7] (Bettler '92) Appeal Nos.: 1998-0217 and 1999-0399.
[8] (Birnbaumer) Appeal No.: 1999-0350.
[9] (Blackstone) Appeal No.: 2000-0440.
[10] (Cutting) Appeal Nos.: 1997-3221, 1997-3377, and 1999-2200.
[11] (Durand) Appeal No.: 2000-0440.

Grandy et al. (Grandy), "Cloning of the cDNA and gene for human D_2 dopamine receptor," Proc. Natl. Acad. Sci., USA, Vol. 86, pp. 9762-766 (1989)[13]

Grenningloh et al. (Grenningloh), "Alpha subunit variants of the human glycine receptor: primary structures, functional expression and chromosomal localization of the corresponding genes," EMBO J., Vol. 9(3), pp. 771-76 (1990)[14]

Keinanen et al. (Keinanen), "A Family of AMPA-Selective Glutamate Receptors," Science, Vol. 249, pp. 556-60 (1990)[15]

McNamara et al., (McNamara), "Chromosomal Localization of Human Glutamate Receptor Genes," J. Neurosci., Vol. 12(7), pp. 2555-562 (1992)[16]

Monyer et al. (Monyer), "Heteromeric NMDA Receptors: Molecular and Functional Distinction of Subtypes," Science, Vol. 256, pp. 1217-221 (1992)[17]

Moriyoshi et al. (Moriyoshi), "Molecular cloning and characterization of the rat NMDA receptor," Nature, Vol. 354, pp. 31-37 (1991)[18]

Nakanishi, "Molecular Diversity of Glutamate Receptors and Implications for Brain Function," Science, Vol. 258, pp. 597-603 (1992)[19]

Puckett et al. (Puckett), "Molecular cloning and chromosomal localization of one of the human glutamate receptor genes," Proc. Natl. Acad. Sci., USA, Vol. 88, pp. 7557-561 (1991)[20]

Schofield et al. (Schofield), "Sequence and expression of human $GABA_A$ receptor $\alpha 1$ and $\beta 1$ subunits," FEBS Letters, Vol. 244(1), pp. 361-64 (1989)[21]
Sommer et al. (Sommer '90), "Flip and Flop: A Cell-Specific Functional Switch in Glutamate-Operated Channels of the CNS," Science, Vol. 249, 1580-585 (1990)[22]

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[12] (Egebjerg) Appeal No.: 1997-3221.
[13] (Grandy) Appeal No.: 1996-3140.
[14] (Grenningloh) Appeal Nos.: 1999-1377, 1999-2200, and 2000-0440.
[15] (Keinanen) Appeal No.: 2000-1780.
[16] (McNamara) Appeal No.: 2000-0440.
[17] (Monyer) Appeal Nos.: 1999-1377 and 2000-0440.
[18] (Moriyoshi) Appeal No.: 1996-3140.
[19] (Nakanishi) Appeal No.: 1999-1377.
[20] (Puckett) Appeal Nos.: 1996-3140, 1997-3221, 1997-3377, 1998-0217, 1999-0350, 1999-0399, 1999-1377, 1999-1393, 1999-2200, 1999-2118, 2000-0440, and 2000-1778.
[21] (Schofield) Appeal Nos.: 1999-1377, 1999-2200, and 2000-0440.

Sommer et al. (Sommer '92), "A glutamate receptor channel with high affinity for domoate and kainate," EMBO J., Vol. 11(4), pp. 1651-656 (1992)[23]

Sugihara et al. (Sugihara), "Structures and Properties of Seven Isoforms of the NMDA Receptor Generated by Alternative Splicing," Biochemical and Biophysical Research Communications, Vol. 185(3), pp. 826-32 (1992)

Sun et al. (Sun), "Molecular cloning, chromosomal mapping, and functional expression of human brain glutamate receptors," Neurobiology, Vol. 89, pp. 1443-447 (1992)[24]

Werner et al. (Werner), "Cloning of a putative high-affinity kainate receptor expressed predominantly in hippocampal CA3 Cells," Nature, Vol. 351, pp. 742-44 (1991)[25]

Zhou et al. (Zhou), "Cloning and expression of human and rat D_1 dopamine receptors," Nature, Vol. 347, pp. 76-79 (1990)[26]

Heinemann et al. (Heinemann) WO 91/06648 May 16, 1991[27]

DISCUSSION

In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995), In re Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993), In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990)(en banc), cert. denied, 500 U.S. 904 (1991),

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[22] (Sommer '90) Appeal Nos.: 2000-1779 and 2000-1780.
[23] (Sommer '92) Appeal No.: 1999-0350.
[24] (Sun) Appeal Nos.: 1997-3221,1999-0350, 1999-1393, 1999-2200, 1999-2118, and 2000-1778.
[25] (Werner) Appeal No.: 1998-0217.
[26] (Zhou) Appeal No.: 1966-3140.
[27] (Heinemann) Appeal Nos.: 1998-0217, 1999-0350, 1999-1393, 1999-2118, 1999-2200, and 2000-1778.

Ex parte Movva, 31 USPQ2d 1027 (Bd. Pat. App. & Int. 1993), and In re Anderson, 391 F.2d 953, 157 USPQ 277 (CCPA 1968) are by far the most relevant in deciding the issues in this family of appeals.

However, we note that obviousness is a legal conclusion based on the underlying facts. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966); Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1270, 20 USPQ2d 1746, 1750 (Fed. Cir. 1991); Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1566-68, 1 USPQ2d 1593, 1595-97 (Fed. Cir. 1987), cert. denied, 481 U.S. 1052 (1987).

To the extent that the examiners and appellants would argue that the cited case law stands for the proposition that a per se rule exits when relying upon so-called methodology in determining the patentability of claims, we point out that, since the decisions in Bell and Deuel, our appellate reviewing court has made it clear that there are no per se rules of obviousness or nonobviousness. In re Ochiai, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995)("reliance on per se rules of obviousness is legally incorrect.") Accord, In re Brouwer, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996).

A per se approach would be in conflict with long standing precedent as to the relevance of the method of making a product to the obviousness of the product. Note In re Payne, ("[a]n invention is not 'possessed' absent some known or obvious way to make it.") citing In re Hoeksema, 399 F.2d 269, 274, 158 USPQ 596, 601 (CCPA 1968). In a similar manner, the court in In re

O'Farrell, 853 F.2d 902, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988), in considering the Polisky reference relative to the rejected claims stated "Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful." (Emphasis added). See also, In re Lalu, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984)("[t]he prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compounds.")

Since there are no per se rules of obviousness or nonobviousness, each case must be decided upon the facts in evidence in that case. See In re Cofer, 354 F.2d 664, 667, 148 USPQ 268, 271 (CCPA 1966)("[n]ecessarily it is facts appearing in the record, rather than prior decisions in and of themselves, which must support the legal conclusion of obviousness under 35 U.S.C. § 103"); and Ex parte Goldgaber, 41 USPQ2d 1172, 1176 (Bd. Pat. App. & Int. 1995)("each case under 35 U.S.C. § 103 is decided on its own particular facts.")

There are no per se rules of obviousness. In re Ochiai, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995).

THE KAINATE CLASS OF GLUTAMATE RECEPTORS

I. The EAA3C & EAA3D Subclass:

Appeal No. 1999-0350[28]
Application No. 08/189,738

Claim 23 is illustrative of the subject matter on appeal and is reproduced below:

23. A method of assaying a test ligand for binding to a human CNS receptor, which comprises the steps of incubating the test ligand under appropriate conditions with a human EAA-3 receptor-producing cell or with a membrane preparation derived therefrom which contains said EAA3 receptor and then determining the extent of binding between the human EAA3 receptor and the test ligand, wherein said cell has been engineered genetically to produce a kainate-binding human EAA receptor having incorporated expressibly therein a heterologous DNA molecule that codes for a human EAA3 receptor selected from the group consisting of: a human EAA3a receptor having the amino acid sequence of SEQ ID NO:2, a human EAA3b receptor having the amino acid sequence of SEQ ID NO:2 with the exception that the amino acid at position 639 is asparagine instead of aspartate, a human EAA3c receptor having the amino acid sequence of SEQ ID NO:17, and a human EAA3d receptor having the amino acid sequence of SEQ ID NO:18.

[28] We recognize appellants' request (Paper No. 25, received May 5, 1997) for oral hearing in this appeal. However, in our review of this appeal we find a hearing is not necessary. 37 CFR § 1.194(c). Accordingly, we make our decision on brief.

GROUNDS OF REJECTION[29]

Claims 23, 25, 26, 37, 39, and 43-45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Heinemann in view of Bettler '90, Sommer '92, Puckett and Birnbaumer.

We reverse.

The rejection under 35 U.S.C. § 103(a):

According to the examiner (Answer[30], page 6):

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate a human homolog of the rat GluR5-2[31] sequence disclosed by Bettler ['90] from a human cDNA library, employing PCR amplification according to Puckett[32], and therewith to assay candidate agonists or antagonists of the human receptor, according to Heinemann, because Bettler ['90] teaches that GluR5 has properties unique among the known glutamate receptors (page 583, col. 2), because Puckett advocates the cloning of human glutamate receptor genes in order to delimit their postulated relationships to a variety of serious pathological conditions, and

[29] We note the Answer contains a single new grounds of rejection over all appealed claims. This new grounds of rejection was made to incorporate Sommer '92 (cited by the examiner (Answer, page 4) as new prior art) into the statement of the rejection.
[30] Paper No. 23, mailed March 4, 1997,
[31] The examiner states (Answer, page 5) that the GluR5-2 cDNA exhibits 86% residue identify with appellants' EAA3a SEQ ID NO:1 at the DNA level and the predicted translation products are 98% identical. The examiner continues that the identity between the rat clone of EAA3b is substantially equivalent to EAA3a except that it differs at only a single nucleotide, resulting in a change at a single amino acid.
[32] The examiner states (Answer, page 5) "Puckett discloses the cloning of a human kainate-binding glutamate receptor, GluHI, which was obtained by PCR amplification using primers derived from the published GluR1 sequence." The examiner states (Answer, page 14) that "Puckett evidences that PCR was a routine and predictable procedure for the retrieval of homologous clones from mammalian cDNA libraries." Puckett does not teach the isolation of GluR1 by use of PCR. Puckett teaches the amplification of a probe [Puckett, page 7557, column 2 and page 7558, Results, column 1] which is then used to screen a cDNA library under reduced stringency hybridization [Puckett, bridging paragraphs, pages 7557-7558 and page 7558, Results, column 1].

> because Birnbaumer teaches that, as was appreciated in the art, receptor agonists or antagonists which are candidate human therapeutics should be assayed with human receptor systems. The artisan would reasonably have expected a human homolog having structural and functional properties similar to GluR5-2 to exist because Puckett teaches that a gene family similar to the GluR gene family in rat will be present in humans; moreover, Puckett exemplifies one clone which exhibits "extreme conservation" of sequence compared to the most closely related rat cDNA. The artisan would reasonably have expected the properties of the human GluR5 gene product to be qualitatively the same as those observed for the rat receptor, including the ability to bind to and respond to kainate, as evidenced by Sommer ['92]. The artisan would also have expected, however, that although qualitatively similar, such properties would likely not be identical because Birnbaumer teaches, as was known in the art, that species-specific variations in the quantitative pharmacological properties are to be expected when comparing homologous gene products. The artisan would have expected to find one <u>or</u> two cDNAs homologous to the rat GluR5-2 in a human cDNA library because of the recognized diploid nature of the human genome: the copies of the gene inherited from different parents could be identical or different. The artisan would have expected that each of the two alleles would be closely related to the rat cDNA. The routineer would have entertained a reasonable expectation of success in isolating and identifying the desired clone(s) because of Heinemann, Bettler ['90], and Sommer ['92] describe several characteristic properties of the receptor (sequence, tissue distribution, functional response in <u>Xenopus</u> and HEK cells, <u>etc.</u>). The practice of the assays disclosed by Heinemann would necessarily involve the assessment of binding between the candidate (ant)agonists and the receptor protein or would alternatively have involved the measurement of phenomena (<u>e.g.</u>, potentiation of electrophysiological properties) which the artisan would have expected to correlate with such binding. The claimed invention would have been <u>prima facie</u> obvious as a whole at the time it was made.

While the claims on appeal are drawn to "[a] method of assaying" it is obviously key to the examiner's rejection that a cDNA encoding the EAA3a, 3b, 3c or 3d receptor must be first successfully isolated. Once isolated the cDNA is used to engineer a cell to express the receptor, and then the claimed method can be performed.

With regard to the examiner's approach, we note that the instant application is a divisional application of Application No. 07/989,793, now abandoned. We further note, United States Patent No. 5,547,855 ('855) is a continuation of 07/989,793, and United States Patent No. 6,018,023 ('023) is a continuation of '855. It appears that the examiner's rejection of the claims in the present application under 35 U.S.C. § 103 is inconsistent with the determination that claims 1, 8 and 17 of '855 are patentable, and claim 1 of '023 is patentable. Claims 1, 8 and 17 of the '855 patent read as follows:

1. An isolated and purified polynucleotide that codes for a kainate- binding human EAA3 receptor selected from the groups consisting of: a human EAA3c receptor having the amino acid sequence of residues 1-836 of SEQ ID NO:17, a human EAA3c receptor having the amino acid sequence of SEQ ID NO:17, a human EAA3d receptor having the amino acid sequence of residues 31-848 of SEQ ID NO:18 and a human EAA3d receptor having the amino acid sequence of SEQ ID NO: 18.

8. A transformed cell having incorporated expressibly therein a heterologous polynucleotide as defined in claim 1, whereby said cell produces said EAA3c or said EAA3d receptor.

17. A membrane-containing preparation derived from a cell as defined in claim 8, wherein said preparation comprises said human EAA3c or human EAA3d receptor.

Claim 1 of the '023 patent reads as follows:

1. A human EAA3 receptor in a form essentially free from other proteins of human origin, selected from the group consisting of:
   a human EAA3a protein having the sequence of amino acids 1-875 of SEQ ID NO: 2; and
   a human EAA3b protein having the sequence of amino acids 1-875 of SEQ ID NO: 2 in which the amino acid residue at position 639 has been replaced by asparagine.

In addition, both patents cite on their face, as considered, prior art relied upon in the present application to support the rejection under 35 U.S.C. § 103[33].

While the examiner may issue a rejection if appropriate under these circumstances, a rejection using the rationale set forth above would appear to require the signature of the Group Director. Compare Manual of Patent Examining Procedure (MPEP) ' 2307.02 (7th ed., July 1998). We note the Group Director did not sign the examiner's action.

Generally, appeals on these facts are remanded to provide the examiner an opportunity to consider the issued patent and determine its effect, if any, on the issues raised under 35 U.S.C. § 103. However, after considering the facts in this case we believe the better course of action is to move forward with a decision on the merits of this appeal.

The initial burden of establishing reasons for unpatentability rests on the examiner. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Furthermore, we note the direction provided by In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991):

> Where the subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. . . . Both the suggestion

[33] The '023 patent cites Heinemann, Sommer, Puckett and Bettler as considered. The '855 patent cites Heinemann, Puckett and Bettler as considered.

> and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In response to the examiner's rejection appellants state (Brief, page 10):

> Given a rat receptor, or any non-human receptor, one of skill may postulate as to the existence of a similar human receptor, but until that receptor is actually isolated, its existence and degree of similarity to the rat receptor with respect to sequence and function, can only be surmised, not reasonably expected.

In our view, in the absence of a reasonable expectation of success of isolating and identifying the specific DNA sequence of the claim, one is left with only an "obvious to try" situation which is not the standard of obviousness under 35 U.S.C. § 103. See In re O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1680.

The examiner (Answer, bridging paragraph, pages 12-13) does not find the argument that a human GluR[5]-2 homology might not exist persuasive. Instead, while noting that "[t]here was no absolute assurance at the time of the invention that a human homolog of GluR[5]-2 could be retrieved from a human library," the examiner finds that the "great preponderance of the evidence of record" in this case expressly suggests that "homologs of the rat glutamate receptors will be found in mammals generally, including humans."

Appellants provide a table (Brief[34], pages 19-20) and explain that GluR5-2 "has only about 97.5% identity with EAA3, including eleven non-conservative substitutions. In addition to the foregoing differences, GluR5-1 of Heinemann/Bettler ['90] has an additional 15 amino acids between residues 371 and 372 of EAA3, and therefore GluR5-1 has only about 96.5% identity with EAA3a or EAA3b[.] including eight non-conservative substitutions." Appellants further identify (Brief, page 20) that "eight of the positions at which EAA3 differs from GluR5 of Heinemann/Bettler ['90] involved serine, i.e., a serine in Heinemann/Bettler ['90] is

[34] Paper No. 22, received November 27, 1996.

changed to something other [than] serine, or something other than serine in Heinemann/Bettler [‘90] is changed to a serine." Appellants conclude (Brief, page 20) that due to serine’s involvement in phosphorylation and glycosylation, “a skilled artisan would not be inclined to make serine substitutions, based on the potential effect of phosphorylation and/or glycosylation on receptor activity.”

In response the examiner states (Answer, page 9) that:

> The presence of non-conservative substitutions in human vs. rat GluR5/EAA3 does not imply unobviousness for one of ordinary skill in the art of molecular biology. … the ordinarily skilled molecular biologist would undertake to use probes or primers based upon the sequence in hand to identify and isolate the desired mammalian homolog, as evidenced, for example, by Puckett.

The examiner concludes (Answer, page 10) that an artisan of ordinary skill “would thus have expected to retrieve a human GluR5-2 homolog having several conservative and nonconservative substitutions relative to the rat sequence.

However, initially, we note that while the claim recites a Markush grouping of four distinct EAA3 receptors, we find nothing in the examiner’s rejection or arguments which reasonably teaches or suggests any one of these specific sequences, identified by SEQ ID Nos. In fact, the examiner expressly states (Answer, page 12) that “[t]here was no absolute assurance at the time of the invention that a human homolog of GluR[5]-2 could be retrieved from a human library.” We further note the examiner indicated (Final Rejection, Paper No. 15, mailed March 27, 1996) claims 41, 42, 46 and 47 as allowable. These claims are limited to methods using the EAA3c and EAA3d receptors.

Notwithstanding this lack of assurance that a human homolog could be successfully retrieved the examiner believes that an artisan of ordinary skill would have expected to retrieve a human GluR5-2 homolog having several conservative and nonconservative substitutions relative to the rat sequence. We are left to guess at which EAA3 subtype (e.g. EAA3a, EAA3b, EAA3c, or EAA3d) this homolog would represent.

In our opinion, more is required than merely a high level of homology between GluR5-2 and EAA3a-b to suggest the use of techniques disclosed by Puckett to obtain DNA encoding any one of EAA3a-d. We compare the factual evidence before us, in this case, with the factual record present in Ex parte Goldgaber, 41 USPQ2d 1172 (Bd. Pat. App. & Int. 1995) where a rejection based on the rationale applied in this case was affirmed. In Goldgaber, in addition to providing the methodology of isolating, identifying and sequencing a DNA that would encode a known polypeptide, the prior art indicated that the polypeptide for which the DNA was sought had been purified and the amino acid sequence was known. (Goldgaber at 1173). There was also information and guidelines as to the preparation of degenerate oligonucleotide probes based upon that known amino acid sequence which would have been useful in the disclosed isolation process. (Id. at 1174). On the record before us, and as argued by appellants, the proteins of the claimed invention were not known to be present in humans. Further, the examiner has provided no evidence which would provide a reasonable suggestion, motivation, or direction which would have led one of ordinary skill in this art to use the techniques of Puckett to isolate and identify the DNA sequences which would

encode such unknown proteins. In re Vaeck, 947 F.2d 488, 494, 20 USPQ2d 1438, 1443-1444 (Fed. Cir. 1991). In re O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1681 (what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it).

The initial burden of presenting a prima facie case of obviousness rests on the examiner. On these facts, it is our opinion that the examiner has failed to provide the evidence necessary to support a prima facie case of obviousness as to the EAA3 receptors used in the claimed assay method.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Kamboj Declaration executed September 29, 1995, relied on by appellants to rebut any such prima facie case.

Accordingly we reverse the examiner's rejection of claims 23, 25, 26, 37, 39, and 43-45 under 35 U.S.C. § 103(a) as being unpatentable over Heinemann in view of Bettler '90, Sommer '92, Puckett and Birnbaumer.

Summary:

We reverse the examiner's rejection of claims 23, 25, 26, 37, 39, and 43-45 under 35 U.S.C. § 103(a) as being unpatentable over Heinemann in view of Bettler '90, Sommer '92, Puckett and Birnbaumer.

REVERSED

II. The EAA4 Subclass:

Appeal No. 1997-3221
Application No. 08/249,241

Claims 26, 27, 28, and 45 are illustrative of the subject matter on appeal and are reproduced below:

26. A method of detecting interaction between a test ligand and a human CNS receptor, which comprises the steps of incubating the test ligand with a human EAA4 receptor-producing cell, or with a membrane preparation derived from said cell, the cell having incorporated expressibly therein a heterologous polynucleotide that encodes a human EAA4 receptor selected from the group consisting of:

    EAA4a having the amino acid sequence of amino acids 1-877 of SEQ ID NO:2, and

    EAA4b having the amino acid sequence of amino acids 1-877 of SEQ ID NO:2 with the exception that the amino acid at position 727 is aspartic acid,

    and then measuring ligand-induced electrical current across said cell or membrane.

27. A method according to claim 26, wherein the receptor-producing cell is an EAA4a receptor-producing cell.

28. A method according to claim 27, wherein the cell is a mammalian cell.

45. A method according to claim 26, wherein the heterologous DNA has a nucleotide sequence of nucleotides 226-2855 of SEQ ID NO:1 with the exception that the guanosine at position 2403 is replace by adenosine.

GROUNDS OF REJECTION[35]

Claims 26, 27, 40, 45 and 47-52 are rejected under 35 U.S.C. § 103 as being unpatentable over Egebjerg in view of either Sun or Puckett.

Claim 28 is rejected under 35 U.S.C. § 103 as being unpatentable over Egebjerg, Puckett and Sun as applied to claim 26, 27, 40, 45 and 47-52 and further in view of Cutting.

We reverse

Claims 26 and 45:

The examiner's basis for this rejection is that it would have been obvious to identify and isolate a nucleic acid encoding the EAA4 receptor subunit, engineer a cell to express this subunit and then obtain a method of assaying as claimed. To support this rejection the examiner references (Answer[36], page 4) Egebjerg (Figure 1, page 746) for a teaching of the rat GluR6 receptor subunit, and a binding assay using a cell expressing this GluR6 receptor subunit. This

[35] We note the Communication from the examiner (Paper No. 18, mailed May 16, 1997) wherein the examiner refused to enter appellants' Reply Brief (Paper No. 17, received March 31, 1997). Appellants' petitioned (Paper No. 19, received July 16, 1997) under 37 CFR § 1.181 the refusal to enter the Reply Brief. The Decision on the Petition (Paper No. 20, mailed August 7, 1997), granting the petition, states in part "[t]he application will be forwarded to the examiner for entry of the reply brief and for any other appropriate action." However, no further action by the examiner was taken in response to the Decision on the Petition. Under these circumstances, we have considered appellants' Reply Brief, rather than remand the application for the examiner to comply with the Decision on the Petition.
[36] Paper No. 16, mailed January 29, 1997.

rat GluR6 receptor subunit was found by the examiner to be 99.5% identical to the amino acid sequence of the receptor subunit of the appealed claims. The examiner references (Answer, bridging paragraph, pages 4-5) Sun and Puckett for a description of the isolation of a DNA encoding human homolog of the rat GluR1.

The examiner further references (Answer, page 6) Puckett for the teaching that "[t]he extreme conservation between the human and rat kainate receptor subunits suggest that a similar gene family will encode human kainate receptors."

While the claims on appeal are drawn to "[a] method of detecting interaction" using a human EAA4 (having a specific SEQ ID NO.) receptor-producing cell. It is obviously essential to the examiner's rejection that a cDNA encoding the EAA4a or 4b receptor must first be successfully isolated. Once isolated the cDNA is used to engineer a cell to express the receptor, and then the claimed method can be performed.

With regard to the examiner's approach, we note that the instant application is a divisional application of Application No. 07/903,456, now United States Patent No. 5,574,144 ('144). It appears that the examiner's rejection of the claims in the present application under 35 U.S.C. § 103 is inconsistent with the determination that at least claims 1, 3, 15, 16 and 18 of '144 are patentable.

Claims 1, 3, 15, 16 and 18 of the '144 patent read as follows:

1. An isolated polynucleotide that codes for the human EAA4 receptor that has the amino acid sequence of amino acids 1-877 of SEQ ID NO:2.

3. An isolated polynucleotide which encodes the human EAA4 receptor that has an amino acid sequence of amino acids 1-877 of SEQ ID NO: 2 with the exception that the amino acid at position 727 is aspartic acid, wherein said human EAA4 receptor is the human EAA4b receptor.

15. A cell that has been engineered genetically to produce a kainate-binding human EAA4 receptor, said cell having incorporated expressibly therein the polynucleotide as recited in claim 1.

16. The cell as defined in claim 15, which is a mammalian cell.

18. The membrane preparation derived from the cell as defined in claim 15.

In addition, both Puckett and Sun relied upon the examiner in this appeal are cited on the face of the patent as considered prior art.

While the examiner may issue a rejection if appropriate under these circumstances, a rejection using the rationale set forth above would appear to require the signature of the Group Director. Compare MPEP ' 2307.02 (7th ed., July 1998). We note the Group Director did not sign the examiner's action.

Generally, appeals on these facts are remanded to provide the examiner an opportunity to consider the issued patent and determine its effect, if any, on the issues raised under 35 U.S.C. § 103. However, after considering the facts in this case we believe the better course of action is to move forward with a decision on the merits of this appeal.

The initial burden of establishing reasons for unpatentability rests on the examiner. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir.

1992). Furthermore, to establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

In response to the examiner's rejection appellants' state (Brief, bridging paragraph, pages 13-14):

> Given a rat receptor, or any non-human receptor, one of skill may postulate as to the existence of a similar human receptor, but until that receptor is actually isolated, its existence and degree of similarity to the rat receptor with respect to sequence and function, can only be surmised, not reasonably expected.

Appellants further provide a table (Brief[37], page 7), and corresponding explanation of the differences between GluR6 and EAA4a and EAA4b.

In the absence of a reasonable expectation of success of isolating and identifying the specific DNA sequence of the claim, one is left with only an "obvious to try" situation which is not the standard of obviousness under 35 U.S.C. § 103. See In re O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1680.

The examiner states (Answer, page 14) "[t]here is no art of record which reports that a human homologue of a known rat neurotransmitter receptor does not exist." The examiner after citing the Puckett reference for its teaching of the conservation in the human and rat kainate receptor subunits, states (Answer, page 13) "[w]hereas it is certain that not every gene which is present in one mammal will have a homologous gene in a second mammal, an artisan had more than a reasonable expectation that humans contain a gene that was homologous to the GluR6 gene." The examiner continues by stating (Answer, bridging paragraph, pages 14-15) that:

[37] Paper No. 15, received November 12, 1996.

> The instant rejection … requires an artisan to have had a reasonable expectation that a DNA encoding a human glutamate receptor subunit which is structurally and functionally homologous to the rodent glutamate receptor subunit GluR6 of the Egebjerg et al. reference could have been isolated by probing a human cDNA library with a DNA encoding that rodent receptor in the manner described in the fourth paragraph on page 7557 of the Puckett et al. publication.

Initially, we note that while the claim recites a Markush grouping of two distinct EAA4 receptors, we find nothing in the examiner's rejection or arguments leading to any one of these specific sequences, identified by SEQ ID NOs. In addition, we note Puckett (page 7561, column 1) which states "[t]he molecular cloning of additional human glutamate receptor genes will be necessary to confirm the conservation of this gene family in humans." This statement by Puckett detracts from the examiner's close adherence to Puckett's statement (Page 7559, column 1) speculating that "a similar diversity [to that found in rats] is likely to be found in human KA receptors."

In our opinion, more is required than merely a high level of homology between GluR6 and EAA4a-4b to suggest the use of techniques disclosed by Puckett to obtain DNA encoding any one of EAA4a-4b, recited in the claim by specific SEQ. ID. NOs. Selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. In re Dow Chem. Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

Comparing the factual evidence before us, in this case, with the factual record present in Ex parte Goldgaber, 41 USPQ2d 1172, 1173 (Bd. Pat. App. & Int. 1995) which affirmed a rejection based on the rationale applied in this case, in

addition to providing the methodology of isolating, identifying and sequencing a DNA which would encode a known polypeptide, the prior art indicated that the polypeptide for which the DNA was sought had been purified and the amino acid sequence was known.

On the record before us, and as argued by appellants, the proteins of the claimed invention were not known to be present in humans, there was only a suggestion by Puckett (Page 7559, column 1) that a similar diversity in rats "is likely to be found in human KA receptors." Further, the examiner has provided no evidence that would provide a reasonable suggestion, motivation, or direction that would have led one of ordinary skill in this art to use the techniques of Puckett to isolate and identify the DNA sequences that encode such unknown proteins. In re Vaeck, 947 F.2d 488, 494, 20 USPQ2d 1438, 1443-444 (Fed. Cir. 1991).

The initial burden of presenting a prima facie case of obviousness rests on the examiner. On these facts, we are constrained to reach the conclusion that the examiner has failed to provide the evidence necessary to support a prima facie case of obviousness as to the EAA4 receptors used in the claimed assay method.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly we reverse the examiner's rejection of claims 26, 27, 40, 45 and 47-52 under 35 U.S.C. § 103 as being unpatentable over Egebjerg in view of Puckett or Sun.

Claim 28:

The examiner's basis for this rejection is substantially the same as that discussed above, except that it adds the teachings of Cutting. According to the examiner (Answer, bridging paragraph, pages 8-9) Cutting teaches:

> [I]ncorporation of a DNA encoding the GABA receptor subunit described therein into an expression vector, the introduction of that expression vector into a mammalian host cell and the preparation of membrane homogenate from those cells for the purpose of determining the binding characteristics of a receptor containing that subunit.

The examiner concludes (Answer, page 9) that "[b]ecause GluR6 was known to be structurally and functionally analogous to the GABA receptor subunit of Cutting" the preparation of membrane homogenate containing GluR6 would have been prima facie obvious.

The examiner failed to establish a prima facie case of obviousness with respect to the combination of Egebjerg in view of Puckett or Sun, supra. Cutting fails to make up for the deficiencies of the combination of Egebjerg in view of Puckett or Sun.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly, we reverse the examiner's rejection of claim 28 under 35 U.S.C. § 103 as being unpatentable over Egebjerg in view of Puckett or Sun as to claims 26, 27, 40, 45, and 47-52 and further in view of Cutting.

Summary:

We reverse the examiner's rejection of claims 26, 27, 40, 45, and 47-52 under 35 U.S.C. § 103 as being unpatentable over Egebjerg in view of either Sun or Puckett.

We reverse the examiner's rejection of claim 28 under 35 U.S.C. § 103 as being unpatentable over Egebjerg, Puckett, and Sun as applied to claim 26, 27, 40, 45, and 47-52 and further in view of Cutting.

REVERSED

III. The EAA5 Subclass:

Appeal No. 1998-0217
Application No. 08/178,019

Claims 35, 37, and 38 are illustrative of the subject matter on appeal and are reproduced below:

35. A method of assaying a test ligand for the ability to bind to a human CNS receptor, said method comprising the steps of
(a) incubating a test ligand with:
a genetically engineered cell that produces a high affinity kainate-binding human EAA5 receptor selected from the group consisting of:
- the human EAA5a receptor encoded by residues 1-888 of SEQ ID NO:2;
- the human EAA5b receptor encoded by residues 1-888 of SEQ ID NO:2 wherein residue 321 is arginine; and
- the human EAA5c receptor encoded by residues 1-838 of SEQ ID NO:2 followed by two proline residues;

said cell having incorporated expressibly therein a heterologous DNA molecule encoding a human EAA5 receptor or, a membrane preparation derived from said cell, wherein said incubation is performed under conditions which permit binding of said test ligand with said human EAA5 receptor; and
(b) determining the extent of binding between said test ligand and said human EAA5 receptor by comparison with kainate-binding to said EAA5 receptor.

37. The method of claim 35, wherein said cell is a mammalian cell.

38. The method of claim 37, wherein said test ligand is incubated with said membrane preparation derived from said human EAA5-producing cell.

GROUNDS OF REJECTION

Claims 35, 37, and 38 are rejected under 35 U.S.C. § 103 as being unpatentable over Bettler in view of Puckett.

Claims 35, 37, and 38 are rejected under 35 U.S.C. § 103 as being unpatentable over Werner in view of Heinemann and Puckett.

We reverse.

Bettler '92 in view of Puckett:

Claim 35:

According to the examiner (Answer[38], bridging paragraph, pages 4-5):

> Given the teachings of Puckett, the skilled artisan would have expected human GluR7 (EAA5a receptor) to be expressed in human brain and to have nucleic acid and amino acid sequences that are highly identical to those of rat GluR7 of Bettler ['92]. Accordingly, it would have been prima facie obvious to the skilled artisan to isolate a cDNA encoding human GluR7 by using the rat GluR7 of Bettler ['92] as a probe to screen the human brain cDNA library of Puckett and to transfect the isolated cDNA into mammalian host cells for production of the receptor.

Thereafter, according to the examiner (Answer, page 5), it would have been obvious at the time the invention was made to modify the assay of Bettler '92 by using the isolated human GluR7 nucleic acid instead of the rat GluR7.

In response to appellants' arguments the examiner states (Answer, page 15) "Bettler ['92] teaches isolation of the cDNA encoding rat GluR7 using the cDNA encoding rat GluR5 as a probe to screen a rat brain cDNA library [page 259]. Thus, the cited references provide sufficient guidance for obtaining the DNA encoding human EAA5a receptor."

We emphasize the examiner's statement that Bettler '92 uses rat GluR5 cDNA as a probe to isolate the rat GluR7 cDNA. This step was performed using low stringency hybridization conditions. Furthermore, the screening method taught by Puckett to isolate human cDNA using a rat cDNA probe also uses reduced stringency conditions (Puckett, bridging paragraph, pages 7557-558, and page 7558, Results, column 1). It appears to us that given the cross-reactivity of the

nucleic acids (e.g. a GluR5 probe detects GluR7) under the low stringency hybridization conditions taught by the references, a person of ordinary skill in this art would reasonably obtain more than the human receptor sought.

In the absence of a reasonable expectation of success of isolating and identifying the specific DNA sequence of the claim, one is left with only an "obvious to try" situation which is not the standard of obviousness under 35 U.S.C. § 103. See In re O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1680.

We note the examiner's statement (Answer, bridging paragraph, pages 15-16) "[s]uccessful isolation of the human GluR7 cDNA requires only a probe that will hybridize to the human GluR7 under conditions routinely used for cloning a desired cDNA." On this record we do not have such a probe that can be used by the conditions taught by the references. Instead we have a teaching that a GluR5 cDNA probe was used to isolate GluR7 cDNA suggesting that the nucleic acid is cross-reactive under the conditions relied upon by the examiner.

Therefore, while appellants, as noted by the examiner (Answer, bridging paragraph, pages 14-15) incorrectly view Puckett as teaching a PCR method for

[38] Paper No. 21, mailed July 3, 1996.

the isolation of their cDNA, we nevertheless agree with appellants' conclusion (Brief[39], page 19) that:

> [A] person of ordinary skill in the art would have appreciated that numerous parameters in the protocol taught by Puckett would have required considerable adjustment for it to be used to isolate polynucleotides encoding a human EAA5 receptor.

While a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the protocol taught by Puckett, the modification is not obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 211 USPQ 1125, 1127 (Fed. Cir. 1984). Here we see no such reason to modify the references as applied.

On this record the examiner relies (Answer, page 4) on the hindsight observation that rat GluR7 of Bettler '92 and the human EAA5a receptor proteins have 97% amino acid sequence identity. However, the examiner has provided no factual evidence that one of ordinary skill in this art could use the techniques of Puckett to isolate and identify the DNA sequences encoding the proteins of the claimed assay method with a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 494, 20 USPQ2d 1438, 1443-444 (Fed. Cir. 1991).

Claim 38:

The examiner states (Answer, page 15) that "the assay of Bettler employs membrane preparation as the source of the rat GluR7 for ligand binding assay, and therefore renders the claims obvious." In our opinion, the examiner failed to meet

[39] Paper No. 19, received January 22, 1996.

her burden of establishing a prima facie case of obviousness in obtaining the necessary nucleic acid to use in obtaining these membrane preparations.

The initial burden of presenting a prima facie case of obviousness rests on the examiner. On these facts, we are constrained to reach the conclusion that the examiner has failed to provide the evidence necessary to support a prima facie case of obviousness as to obtaining EAA5 cDNAs. Without first successfully obtaining the cDNAs the examiner's basis for rejecting the claimed method of assaying can not be supported.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly we reverse the examiner's rejection of claims 35-38 under 35 U.S.C. § 103 as being unpatentable over Bettler '92 in view of Puckett.

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Kamboj Declaration executed May 3, 1994, relied on by appellants to rebut any such prima facie case.

Werner in view of Heinemann and Puckett:

Claim 35:

The examiner's basis for this rejection is similar to that made for Bettler '92 in view of Puckett, supra. Specifically, that it would have been prima facie obvious to a person of ordinary skill in the art to obtain the relevant nucleic acid and then express that nucleic acid in a cell, or on a cell membrane in such a manner that an assay can be performed.

In establishing this rejection the examiner states (Answer, bridging paragraph, pages 6-7) that "it would have been obvious to the skilled artisan to isolate the cDNA encoding human GluR7 (EAA5a receptor) by using the cDNA encoding rat GluR7 of Heinemann as a probe to screen a human brain cDNA library, as taught by Heinemann." The examiner states (Answer, page 6) that "Heinemann teaches isolation of the cDNA encoding rat GluR7 using the cDNA encoding rat GluR5 as a probe to screen a rat brain cDNA library (page 40)." Heinemann (page 40, Example 19) teaches that "cDNA clones encoding the GluR6 and GluR7 genes were isolated from a[n] adult rat forebrain library using a low-stringency hybridization screening protocol … and … GluR5 cDNA as probe."

This again emphasizes the cross-reactivity and resulting unpredictability associated with isolating an EAA5 cDNA (having the claimed SEQ ID NOs) according to the methodology set forth by the examiner.

Claim 38:

The examiner relies upon Werner to teach binding assays. However, the examiner again fails to provide the factual evidence necessary to demonstrate that a person of ordinary skill would have a reasonable expectation of success in obtaining the nucleic acid necessary to perform the claimed assay method. Therefore, in our opinion, the examiner failed to meet her burden of establishing a prima facie case of obviousness in obtaining the necessary nucleic acid to use in obtaining these membrane preparations.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Kamboj Declaration executed May 3, 1994, relied on by appellants to rebut any such prima facie case.

Accordingly, we reverse the examiner's rejection of claims 35-38 under 35 U.S.C. § 103 as being unpatentable over Werner in view of Heinemann and Puckett.

New Grounds of Rejection under 37 CFR § 1.196(b):

Claims 35-38 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of assaying comprising the steps of incubating a test ligand with a genetically engineered cell that produces "a high affinity kainate-binding" human EAA5 receptor. The specification as originally filed does not describe the human EAA5 receptor subunit as a high affinity kainate binding polypeptide, and the claims as originally filed do not recite the term "high affinity kainate-binding." Example 3 of the specification shows that the human EAA5a receptor subunit binds kainate, but example 3 does not show that the receptor subunit is a high affinity kainate-binding polypeptide. Thus, the specification does not reasonably convey to the skilled artisan that the inventor, at

the time the application was filed, had possession of a polynucleotide encoding a high affinity kainate binding human EAA5 receptor subunit, and thereby did not have a method of assaying a test ligand using a genetically engineered cell that produces a high affinity kainate-binding human EAA5 receptor.

We note that a rejection based on these facts was made in the Examiner's Answer of Application No. 08/377,503 (Appeal No. 1999-0399). In response to this ground of rejection appellants' amended the claim to remove the term "high affinity."

Time Period for Response for Appeal No. 1998-0217:

This opinion in Appeal No. 1998-0217 contains a new ground of rejection pursuant to 37 CFR § 1.196(b). 37 CFR § 1.196(b) provides that, "[a] new ground of rejection shall not be considered final for purposes of judicial review."

37 CFR § 1.196(b) also provides that the appellants, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the two following options with respect to the new ground of rejection to avoid termination of proceedings (§ 1.197(c)) as to the rejected claims:

> (1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner ….
>
> (2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record ….

Summary:

We reverse the examiner's rejection of claims 35, 37 and 38 under 35 U.S.C. § 103 as being unpatentable over Bettler in view of Puckett.

We reverse the examiner's rejection of claims 35, 37 and 38 under 35 U.S.C. § 103 as being unpatentable over Werner in view of Heinemann and Puckett.

We make the following New Ground of Rejection under 37 CFR § 1.196(b). Claims 35-38 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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

REVERSED, 37 CFR § 1.196(b)

Appeal No. 1999-0399
Application No. 08/377,503

Claim 1[40] is illustrative of the subject matter on appeal[41] and is reproduced below:

1. An isolated polynucleotide that codes for a kainate-binding human EAA5 receptor, wherein said receptor is:

   the human EAA5a receptor having the amino acid sequence of residues 1-888 of SEQ ID NO:2;

   the human EAA5b receptor having the amino acid sequence of residues 1-888 of SEQ ID NO:2 except that residue 321 is arginine; or

   the human EAA5c receptor having the amino acid sequence of residues 1-838 of SEQ ID NO:2 followed by Pro-Pro.

Claim 10 is limited to a recombinant DNA construct, wherein said construct is plasmid pcDNAI/humEAA5a (ATCC 75296). Claim 17 is limited to a membrane preparation derived from a cell transfected with a heterologous DNA that encodes for EAA5a, EAA5b or EAA5c as described in claim 1 with the exception that the EAA5c receptor instead of followed by two proline residues instead of the specific "Pro-Pro" sequence of defined in claim 1.

[40] Claim 1 was amended after final (Paper No. 36, received July 14, 1997). The above reproduction of claim 1 includes this amendment.
[41] We note the examiner's clarification (Answer, page 4) of applicants' Appendix of appealed claims wherein the examiner states that "line 2 of claim 10, "7" should be replaced with "9".

GROUNDS OF REJECTION[42]

Claims 1, 2, 8-21 and 40 are rejected under 35 U.S.C. § 103 as being unpatentable over Bettler '92 in view of Puckett[43].

We reverse.

Claim 1:

The examiner states (Answer[44], page 8) that:

> [I]t would have been prima facie obvious to the skilled artisan at the time the invention was made to isolate the cDNA encoding human GluR7 (EAA5) by using the nucleic acid of rat GluR7 of Bettler ['92] as a probe to screen a human brain cDNA library, as taught by Puckett, in order to obtain large quantities of human GluR7 by subcloning the isolated nucleic acid into an expression vector and transfecting the expression vector into a host cell such as Hela cells or Xenopus oocytes.

We emphasize the examiner's statement to use the rat GluR7 nucleic acid as a probe to screen a human brain cDNA library as taught by Puckett. The screening method taught by Puckett uses reduced stringency conditions (Puckett, bridging paragraph, pages 7557-558, and page 7558, Results, column 1). Bettler '92 teaches (page 259, column 1) that "[t]he coding region of the GluR5 cDNA clone was used as a probe to screen a rat cerebellum cDNA library under low stringency hybridization conditions … [o]ne cDNA clone encoding part

[42] We note the examiner's new ground of rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph made in the Answer, was withdrawn by the examiner in the Supplemental Answer (Paper No. 37, mailed September 19, 1997.
[43] We note the examiner withdrew her reliance on Heinemann that was applied in the Final Rejection (Paper No. 27, mailed June 6, 1996) in the alternative with Bettler '92 in view of Puckett.
[44] Paper No. 35, mailed May 13, 1997.

of the GluR7 open reading frame was identified." It appears to us that given the cross-reactivity of the nucleic acids under low stringency hybridization conditions, a person of ordinary skill in this art would reasonable obtain more than the human receptor sought.

In the absence of a reasonable expectation of success of isolating and identifying the specific DNA sequence of the claim, one is left with only an "obvious to try" situation which is not the standard of obviousness under 35 U.S.C. § 103. See In re O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1680.

Therefore we agree with appellants' argument (Brief, page 24) that:

> At most, Puckett would have provided the person of ordinary skill in the art with a starting point for developing a generally suitable methodology for isolating a targeted polynucleotide from a DNA library. The reference would not have provided a method that reasonably would have been expected to yield a polynucleotide encoding a human EAA5 receptor in accordance with the claimed invention.

O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1681 (what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it).

The examiner relies (Answer, page 6) on the observation that rat GluR7 of Bettler '92 and the human EAA5a receptor proteins have 97% sequence identity. However, after pointing out the difference between rat GluR7 and human EAA5 (Brief[45], pages 26-28) appellants' argue (Brief, page 28) "[t]he fact that, in hindsight,

[45] Paper No. 34, received February 6, 1997.

the sequence of GluR7 appears to be the rat counterpart of EAA5, is irrelevant to the issue of obviousness."

In our opinion, more is required than merely a high level of homology between GluR7 and EAA5a to suggest the use of techniques disclosed by Puckett to obtain DNA encoding any one of EAA5a-5c, identified in the claim by specific SEQ. ID. NOs. Selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. In re Dow Chem. Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531-532 (Fed. Cir. 1988).

Comparing the factual evidence before us, in this case, with the factual record present in Ex parte Goldgaber, 41 USPQ2d 1172 (Bd. Pat. App. & Int. 1995) affirming a rejection based on the rationale applied in this case. In Goldgaber, in addition to providing the methodology of isolating, identifying and sequencing a DNA that would encode a known polypeptide, the prior art indicated that the polypeptide for which the DNA was sought had been purified and the amino acid sequence was known. (Goldgaber at 1173). There was also information and guidelines as to the preparation of degenerate oligonucleotide probes based upon that known amino acid sequence which would have been useful in the disclosed isolation process. (Id. at 1174). Here the examiner notes (Answer, page 6) that Bettler '92 "does not disclose the nucleic acids encoding human EAA5a and EAA5b receptors." On the record before us, and as argued by appellants, the proteins of the claimed invention were not known to be present in humans, there was only a suggestion by Puckett (page 7559, column 1) that a similar diversity in rats "is likely to be found in human KA receptors," which Puckett

later refines (page 7561, column 1) by stating "[t]he molecular cloning of additional human glutamate receptor genes will be necessary to confirm the conservation of this gene family in humans." Further, the examiner has provided no evidence which would provide a reasonable suggestion, motivation, or direction which would have led one of ordinary skill in this art to use the techniques of Puckett to isolate and identify the DNA sequences which would encode such unknown proteins. In re Vaeck, 947 F.2d 488, 494, 20 USPQ2d 1438, 1443-444 (Fed. Cir. 1991). As noted above, Bettler '92 teaches receptor nucleic acid cross-reactivity using low stringency hybridization.

The initial burden of presenting a prima facie case of obviousness rests on the examiner. On these facts, we are constrained to reach the conclusion that the examiner has failed to provide the evidence necessary to support a prima facie case of obviousness as to the claimed EAA5 DNA compounds.

Claim 10:

The examiner states (Answer, page 8) that "[t]he expression vector containing the nucleic acid encoding human GluR7 would be an obvious variant of the plasmid recited in claims 10 and 40."

Having determined that the examiner failed to meet the burden of establishing a prima facie case for obviousness for obtaining the claimed isolated polynucleotide, we are unable to find any reason, suggestion, or motivation in the

examiner's basis for the rejection to lead an inventor to combine the references to obtain a DNA construct (claim 10), or cell containing such a construct (claim 40). Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

Claim 17:

The examiner states (Answer, page 22) that "Bettler teaches membrane preparations for ligand binding assays … [t]hus, transfected cells comprising the human GluR7 and membrane preparation of such cells, both obtained by following the teachings of Bettler ['92] and Puckett, are obvious over the prior art."

In our opinion, supra, the examiner failed to meet her burden of establishing a prima facie case of obviousness in obtaining the claimed DNA compounds. Without these compounds a membrane preparation derived from a cell transfected with these constructs would not be available.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Kamboj Declaration executed May 3, 1994, relied on by appellants to rebut any such prima facie case.

Accordingly we reverse the examiner's rejection of claims 1, 2, 8-21, and 40 under 35 U.S.C. § 103 as being unpatentable over Bettler '92 in view of Puckett.

Summary:

We reverse the examiner's rejection of claims 1, 2, 8-21 and 40 under

35 U.S.C. § 103 as being unpatentable over Bettler ‘92 in view of Puckett.

REVERSED

THE AMPA CLASS OF GLUTAMATE RECEPTORS

I. The GLUR1 Subclass:

Appeal No. 1997-3377
Application No. 08/216,326

Claims 31, 34 and 39 are illustrative of the subject matter on appeal and are reproduced below:

31. A method of assaying a test ligand for the ability to bind to a human CNS receptor, said method comprising the steps of:
(a) incubating said test ligand with:
(i) a genetically engineered cell that produces an AMPA-binding human receptor GluR1B having the amino acid sequence of residues 1-888 of SEQ ID NO:2, said cell having incorporated expressibly therein a heterologous DNA molecule encoding the human GluR1B, said cell further comprising a membrane, wherein said membrane comprises said human GluR1B, or
(ii) a membrane preparation comprising human GluR1B derived from said cell,
wherein said incubation is performed under conditions which permit binding of said test ligand with said human GluR1B; and
(b) determining the extent of binding between said test ligand and said human GluR1B.

34. The method of claim 33, wherein said test ligand is incubated with said membrane preparation derived from said human GluR1B-producing cell.

39. The method of claim 31, wherein said cell comprises a 3.2 kilobase EcoR1/EcoR1 fragment of the plasmid pBS/human GluR1B (ATCC 75246).

GROUNDS OF REJECTION

Claims 31, 33, 34 and 37-40 are rejected under 35 U.S.C. § 103 over Puckett in view of Cutting.

We reverse.

Claim 31:

The examiner states (Answer[46], page 5) that:

> Cutting et al. clearly shows that every element of the claimed method, except for the particular DNA employed therein, was known in the art in the combination claimed prior to the making of the instant invention. To have incorporated a cDNA encoding a human glutamate receptor subunit like the one that was described by Puckett et al., or any functionally equivalent allelic variant thereof, in place of the cDNA of Cutting et al. to permit the characterization of the human glutamate receptor encoded thereby would have been prima facie obvious to an artisan of ordinary skill in the art of molecular biology in view of this combination of references at the time that the instant invention was made.

With regard to the Puckett sequence, the examiner states (Answer, page 4):

> Because the cDNAs encoding the glutamate receptor subunit of the instant invention and GluH1 of Puckett et al. were both isolated from human brain cDNA libraries by probing those libraries with a DNA probe encoding part of the rat receptor subunit GluR1 and because the amino acid sequence encoded thereby are identical in 898 out of 906 amino acid residues (99.1%, including signal sequence) it is more than reasonable to conclude that they are nothing more than allelic variants of the same protein and, in the absence of unexpected properties, either of these DNAs would have been prima facie obvious in view of the other at the time of the instant invention.

The claims on appeal are drawn to "[a] method of assaying a test ligand" using a human GluR1B (having a specific SEQ ID NO.) receptor-producing cell, or membrane preparation. However, it is obviously essential to the examiner's rejection that a cDNA encoding the GluR1B receptor must first be successfully isolated. Once isolated the cDNA is used to engineer a cell to express the receptor, and then the claimed method can be performed.

[46] Paper No. 18, mailed September 23, 1996.

With regard to the examiner's approach, we note that the instant application is a divisional application of Application No. 07/896,611, now abandoned. Application No. 08/254,573, now United Sates Patent No. 5,610,032 ('032) is a direct continuation of 07/896,611. It appears that the examiner's rejection of the claims in the present application under 35 U.S.C. § 103 is inconsistent with the determination that the claims of '032 are patentable. For example, claims 1, 8, 9 and 10 of the '032 patent read as follows:

1. An isolated polynucleotide which encodes a protein having the sequence of SEQ ID NO:2.

8. A cellular host having incorporated therein a heterologous polynucleotide which encodes a protein having the sequence of SEQ ID NO: 2.

9. A cellular host according to claim 8, which is a mammalian cell.

10. A membrane preparation derived from a cellular host as defined in claim 9.

In addition, Puckett relied upon the examiner in this appeal is cited on the face of the patent as considered prior art.

While the examiner may issue a rejection if appropriate under these circumstances, a rejection using the rationale set forth above would appear to require the signature of the Group Director. Compare MPEP ' 2307.02 (7th ed., July 1998). We note the Group Director did not sign the examiner's action.

Generally, appeals on these facts are remanded to provide the examiner an opportunity to consider the issued patent and determine its effect, if any, on the

issues raised under 35 U.S.C. § 103. However, after considering the facts in this case we believe the better course of action is to move forward with a decision on the merits of this appeal.

The initial burden of establishing reasons for unpatentability rests on the examiner. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Furthermore, to establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Appellants argue (Brief[47], page 5) that the amino acid sequence of the human GluR1B receptor as recited in the claims is not taught by Puckett. Appellants provide a table (Brief, page 6) highlighting the differences between Puckett and SEQ ID NO:2.

In response the examiner states (Answer, bridging paragraph, pages 7-8):

> The simple fact that the nucleotide sequence of the DNA encoding the human glutamate receptor subunit of Puckett et al. is different from the DNA sequence of the instant invention does not defeat the instant rejection since the prior art of record provided a structurally similar composition and the motivation to isolate any analogous compound from any human brain cDNA library. The fact that this property differs slightly and inconsequentially from individual to individual does not support patentability since these difference[s] are the innate differences between naturally occurring compounds and do not constitute an inventive contribution by [a]ppellant.

We remind the examiner that generalization is to be avoided insofar as specific structures are alleged to be prima facie obvious one from the other.

[47] Paper No. 17, received June 25, 1996.

In re Jones, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

An essential component of the examiner's rejection and the claimed invention is that a nucleotide sequence be available to engineer a cell to produce the human receptor GluR1B having the amino acid sequence of residues 1-888 of SEQ ID NO:2. Given the recognition in the '032 patent that any polynucleotide encoding GluR1B having the amino acid sequence of residues of SEQ ID NO:2 is patentable. We find the examiner's rejection of the claimed method of assaying in conflict with In re Pleuddemann, 910 F.2d 823, 828, 15 USPQ2d 1738, 1742 (Fed. Cir. 1990)(reversing a rejection under 35 U.S.C. § 103 of a method claim which uses appellants' new compounds, which constitute the essential limitation of the claims).

Furthermore, we do not agree with the examiner's speculation that "it is more than reasonable to conclude that they [the sequence required by the claimed invention, and Puckett's sequence] are nothing more than allelic variants of the same protein" and that "either of these DNAs would have been prima facie obvious in view of the other at the time of the instant invention." We remind the examiner that "[t]he Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because it may doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis." In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968).

By suggesting that Puckett's sequence and the claimed sequence are "nothing more than allelic variants" where one is "obvious in view of the other," the examiner not only speculates that the differences are a result of allelic variation, but the examiner is essentially adopting a per se rule that among the genus of allelic variants every species is obvious. This is clearly in error. Every case, particularly

those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts. In re Jones, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

Puckett teaches (page 7560, bridging paragraph, columns 1-2) that:

> Many of the amino acid differences (9 of 25 amino acids) between GluHI and GluRI are in a single 38-amino acid region defined by Sommer et al ['92].… In rodent KA receptors this region is encoded by alternatively spliced exons…. The alternative splicing of the exons encoding this region produces KA-sensitive receptor subunits with different agonist and desensitization profiles. Sommer et al. ['92] …have designated these different types of receptor subunits "flip" and "flop." The human cDNA encoding GluHI would be considered as the flip counterpart to the flop version of the rodent clone GluRI…. The conservation of the sequences encoding the flip type of receptor in GluHI suggests that the alternative splicing of similar exons will be used in human glutamate receptor genes.

Thus, as appellants argue (Brief, page 6) "[g]iven the teachings of Puckett, one of skill in the art would not have known that a human GluR1B existed, or that the alterations noted … could have been made to the GluH1 to yield a functional AMPA-binding receptor."

Here, we agree with the appellants that there is no teaching or suggestion in the applied prior art of the GluR1B receptor having the amino acid sequence of residues 1-888 of SEQ ID NO:2 as required by the claim. In re Ochiai, 71 F.3d 1565, 1570, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). We also do not find that there was a reasonable expectation that one could have obtained such a receptor sequence required to perform the claimed methods. In re O'Farrell, 858 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)(obviousness also requires a "reasonable expectation of success").

Claim 34:

In our opinion, supra, the examiner failed to meet his burden of establishing a prima facie case of obviousness in obtaining the GluR1B receptor having the amino acid sequence of residues 1-888 of SEQ ID NO:2. Therefore, a method of assaying, using a membrane preparation derived from a human GluR1B-producing cell would also not have been prima facie obvious.

Claim 39:

In response to appellants' argument that the limitations of claims 39 and 40 were not separately addressed, the examiner states (Answer, page 10) that "[a]ppellant has failed to indicate how these additional limitations provide a patentable contribution over the sequence limitations of the other claims."

We remind the examiner that the burden of establishing unpatentability rests on the examiner. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). In this instance the examiner is attempting to shift the burden to appellants to prove patentability. This is clearly improper.

We find nothing in the examiner's Answer which demonstrates that the combination of references relied upon render a method of assaying, (1) "wherein said cell comprises a 3.2 kilobase EcoR1/EcoR1 fragment of the plasmid pBS/human GluR1B (ATCC 75246)" (claim 39) or (2) "wherein said cell has incorporated expressibly therein a heterologous DNA molecule having the nucleotide sequence 116-2779 of SEQ ID NO:1" (claim 40).

Therefore, in addition to those reasons provided above, we find that the examiner failed to meet his burden of establishing a prima facie case of unobviousness.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly we reverse the examiner's rejection of claims 31, 33, 34 and 37-40 under 35 U.S.C. § 103 over Puckett in view of Cutting.

Summary:

We reverse the examiner's rejection of claims 31, 33, 34 and 37-40 under 35 U.S.C. § 103 over Puckett in view of Cutting.

REVERSED

II. The GLUR2 Subclass:

Appeal No. 1999-1393
Application No. 08/242,344

Claims 1 and 2 are illustrative of the subject matter on appeal and are reproduced below:

1. An isolated polynucleotide that encodes human GluR2B.

2. An isolated polynucleotide according to claim 1, that encodes human GluR2B having amino acid sequence SEQ ID NO:2.

GROUNDS OF REJECTION

Claims 1-16 are rejected under 35 U.S.C. § 103 over Heinemann in view of Puckett and Sun.

We reverse.

The rejection under 35 U.S.C. § 103:

The examiner states (Answer[48], bridging paragraph, pages 8-9) that:

> The isolation of a cDNA encoding the human counterpart of the rat GluR2 subunit that was described in the Heinemann et al. publication by probing the cDNA library of Sun et al. or Puckett et al., each of which was constructed from mRNA isolated from human brain, with a nucleic acid probe encoding all or part of rat GluR2 in a manner that was directly analogous to the method described by Puckett et al. to facilitate the recombinant expression and characterization of the encoded product in the absence of other human glutamate receptor subunits for those reasons that were expressly given by Sun et al. would have been prima facie obvious to an artisan of ordinary skill in the art of molecular biology at the time that the instant invention was made. Given the high level of sequence conservation between rat and human GluR1s as disclosed in each of the Sun et al. and Puckett et al. references and the high degree of sequence and structural similarity between the rat GluR1 and GluR2 subunits as disclosed by Heinemann et al., an artisan had more than a reasonable expectation that the GluR2 of Heinemann et al. was

[48] Paper No. 22, mailed January 13, 1998.

> predictive of the existence, structure and function of an analogous human glutamate receptor subunit. Further, since Sun et al. disclosed a manner through which a cDNA encoding two-thirds of human GluR2 had been isolated and the chromosomal location of the corresponding gene, an artisan would have been certain that a cDNA encoding the entire human GluR2 subunit could be isolated by employing those methods which were routine in the art at the time of the instant invention.

Initially, we note that the instant application shares the same parent with Application No. 08/483,327, now United States Patent No. 6,040,175 ('175). It appears that the examiner's rejection of the claims in the present application under 35 U.S.C. § 103 is inconsistent with the determination that claim 3 of '175 is patentable. Claim 3 of the '175 patent reads as follows:

> 3. The human GluR2B receptor having the sequence of amino acids 1-863 of SEQ ID NO:2, in a form essentially free from other proteins of human origin.

In addition, Heinemann, Puckett, and Sun relied upon by the examiner in this appeal are cited on the face of the patent as considered prior art.

While the examiner may issue a rejection if appropriate under these circumstances, a rejection using the rationale set forth above would appear to require the signature of the Group Director. Compare MPEP ' 2307.02 (7th ed., July 1998). We note the Group Director did not sign the examiner's action.

Generally, appeals on these facts are remanded to provide the examiner an opportunity to consider the issued patent and determine its effect, if any, on the issues raised under 35 U.S.C. § 103. However, after considering the facts in this case we believe the better course of action is to move forward with a decision on the merits of this appeal.

The initial burden of establishing reasons for unpatentability rests on the examiner. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Furthermore, to establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Claim 1:

Appellants argue (Brief[49], page 7) that "[t]he teachings of a single instance of similarity between a rat and human glutamate receptor is not predictive even of the existence, let alone the structure and function, of an analogous human molecule for each rat receptor or gene." [emphasis removed].

The examiner states (Answer, page 12) that "Sun et al. disclosed a cDNA encoding two-thirds of the human GluR2 subunit of the instant invention, making it particularly relevant to the instant rejection." Specifically, Sun (abstract) identifies "a second clone, HBGR2, contains approximately two-thirds of the coding region of a receptor homologous to rat brain clone GluR2." Sun teaches (page 1443, Materials and Methods, column 2) that a probe was amplified using two PCR primers derived from GluR1. This probe was then used (Sun, page 1444, bridging paragraph, columns 1-2) for "[h]ybridization screening [of a human brain cDNA library] at high stringency." This screen yielded four positive clones, derived from two different transcripts. The first clone was found to be

[49] Paper No. 21, received November 26, 1997.

homologous to rat GluR1, the second clone was found to be homologous to GluR2. Sun, page 1444, bridging paragraph, columns 1-2. Sun localizes the HBGR2-encoding gene on chromosome 4q25-34.3. Sun does not disclose any specific sequence for GluR2.

At this point we find that under high stringency hybridization conditions, a probe for GluR1 cross-reacts with GluR2. Little more is provided in Sun, other than the "note" at page 1447 which states "[a]fter submission of this manuscript a paper [referring to Puckett] appeared reporting … GluH1. This cDNA shows differences with HBGR1 … in a region corresponding to the alternatively spliced exon identified in the rodent clones by Sommer ['92] … and designated as flip and flop forms of GluR1." So not only is there cross-reactivity between the receptors, there is also the possibility of alternative splicing events.

Puckett, relied upon by the examiner (Answer, page 6) to teach isolation of human GluR1, teaches the use of a reduced stringency hybridization (bridging paragraph pages 7557-558). Furthermore, Puckett also teaches the existence of alternative splicing events (page 7560, column 1), later confirmed by Sun's "note," supra.

The examiner relies upon Heinemann to teach GluR2 (Answer, page 4). We note Heinemann's Example 8 (page 27) which teaches "cDNA clones encoding the GluR2 and GluR3 genes were isolated from an adult rat forebrain library using a low-stringency hybridization screening protocol … and a radiolabeled fragment of the GluR1 cDNA as [a] probe."

Thus a GluR1 probe cross-reacts with GluR2 and GluR3. Heinemann further teaches that a GluR2 probe cross-reacts with GluR4 and GluR5 (Heinemann, Example 14, page 33).

Here the examiner compares appellants' disclosed sequence with that of the prior art and finds that the human receptor GluR2 is 98.9% identical to the rat receptor (Answer, bridging paragraph, pages 5-6). However, without prior knowledge of appellants' sequence, the degree of identity between the claimed human GluR2B and rat GluR2 was unknown. "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." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

Given the degree of cross-reactivity between at least GluR1-5 (as taught by the prior art of record), and the existence of alternative splicing variants amongst these receptors, we can not agree with the examiner that "an artisan would have been certain that a cDNA encoding the entire human GluR2 subunit could be isolated by employing those methods which were routine in the art at the time of the instant invention." Those methods routine in the art were used to identify GluR1-5 as discussed in the prior art relied upon by the examiner. We do not disagree that given the apparent cross-reactivity of these receptor nucleic

acids that an artisan would have certainly identified something. That, based on this record, a skilled artisan would reasonably have expected to isolated GluR2, we can not agree.

Claim 2:

Appellants' argue (Brief, pages 13-14) that the GluR2B receptor claimed differs from the receptor of the prior art.

The examiner, inter alia, states (Answer, page 18) the "cDNAs of the instant invention are chemical compounds which were present in each of the cDNA libraries of Puckett et al. and Sun et al. … [a]ppellant's inventive contribution was the isolation and characterization of one of these pre-existing compounds and its use in the production of the other." We agree. However, the examiner is reminded that "[t]he 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." In re Dow Chemical Co. 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). In our opinion, on this record, a person of ordinary skill in the art would not have a reasonable expectation of success in obtaining the claimed invention.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Zimmerman Declaration

executed July 21, 1997, and the Declarations[50] filed under 37 CFR § 1.131 of Kamboj (executed August 7, 1997), Nutt (executed June 26, 1997) and Elliott (executed June 26, 1997) relied on by appellants to rebut any such prima facie case.

Accordingly, we reverse the rejection of claims 1-16 under 35 U.S.C. § 103 over Heinemann in view of Puckett and Sun.

Summary:

We reverse the examiner's rejection of claims 1-16 under 35 U.S.C. § 103 over Heinemann in view of Puckett and Sun.

REVERSED

[50] However, we compare the examiner's statement (Answer, page 26) that "[t]he transmission of confidential information does not show a reduction to practice of the claimed isolated DNA," with similar statements made in Appeal Nos.: 1999-2118, 1999-2200, 2000-1778, 2000-1779, and 2000-1780.

Appeal No. 1999-2118[51]
Application No. 08/439,946

Claims 22 and 31 are illustrative of the subject matter on appeal[52] and are reproduced below:

22. A method of assaying interaction between a test ligand and a human CNS receptor, which comprises the steps of incubating the test ligand under appropriate conditions with a cellular host having incorporated expressibly therein a heterologous polynucleotide that encodes human GluR2B comprising the amino acid sequence of amino acids 1-863 of SEQ ID NO:2, or with a membrane preparation derived from said cellular host, and determining the extent of interaction between the human GluR2B and the test ligand.

31. A method according to claim 22, wherein said cellular host is a mammalian cell.

GROUNDS OF REJECTION

Claims 22, 32 and 34-40 are rejected under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett and Sun.

Claims 31 and 33 are rejected under 35 U.S.C. § 103 as being unpatentable over Heinemann, Puckett and Sun as applied to claims 22, 32 and 34-40 above and further in view of Cutting.

We reverse.

[51] We recognize appellants' request (Paper No. 39, received May 18, 1999) for oral hearing in this appeal. However, in our review of this appeal we find a hearing is not necessary. 37 CFR § 1.194(c). Accordingly, we make our decision on brief.
[52] We note the examiner's statement (Answer, page 2) regarding the errors contained in appellants' Appendix of claims.

The rejections under 35 U. S.C. § 103:

Initially, we note that the instant application shares the same parent with Application No. 08/483,327, now United States Patent No. 6,040,175 ('175). It appears that the examiner's rejection of the claims in the present application under 35 U.S.C. § 103 is inconsistent with the determination that claim 1 of '175 is patentable. Claim 1 of the '175 patent reads as follows:

> 1. A membrane preparation derived from a host cell, said host cell having incorporated expressibly therein a heterologous polynucleotide that encodes human GluR2B receptor selected from the group consisting of: (a) the sequence of amino acids 1-863 of SEQ ID NO:2, (b) a human GluR2B receptor variant having a sequence of amino acids 1-863 of SEQ ID NO:2 with the exception that there are from 1-32 conservative amino acid substitutions, (c) a membrane-bound fragment of the human GluR2B receptor of (a) or (b) comprising the extracellular N-terminal region that precedes TM-1, and (d) a membrane-bound fragment of the human GluR2B receptor of (a) comprising the extracellular C-terminal region that follows TM-4.

In addition, Heinemann, Puckett and Sun relied upon by the examiner in this appeal are cited on the face of the patent as considered prior art.

While the examiner may issue a rejection if appropriate under these circumstances, a rejection using the rationale set forth above would appear to require the signature of the Group Director. Compare MPEP ' 2307.02 (7th ed., July 1998). We note the Group Director did not sign the examiner's action.

Generally, appeals on these facts are remanded to provide the examiner an opportunity to consider the issued patent and determine its effect, if any, on the issues raised under 35 U.S.C. § 103. However, after considering the facts in this

case we believe the better course of action is to move forward with a decision on the merits of this appeal.

The initial burden of establishing reasons for unpatentability rests on the examiner. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Furthermore, to establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Claim 22:

The examiner states (Answer[53], bridging paragraph, pages 6-7) that:

> Because a practitioner of the art of molecular biology was well aware that the ultimate value of a glutamate receptor subunit like those of Heinemann et al. would lie in the applicability of the data derived therefrom to human subjects, as evidenced by the statements of Sun et al., that artisan would have found the isolation of a DNA encoding the entire human counterpart of the rat GluR2 that was disclosed in the Heinemann et al. publication by probing a human cDNA library with a rat nucleic acid probe in a manner that was directly analogous to the one described by Puckett et al. to facilitate the recombinant expression and characterization of the encoded product in the absence of other human glutamate receptors for those reasons disclosed by Sun et al. to have been prima facie obvious to an artisan of ordinary skill in the art of molecular biology at the time the instant invention was made.

Appellants discuss the differences between the GluR2B receptor recited in the instant claims and the prior art, and argue (Brief[54], pages 13-15) that "[t]he art fails to suggest not only the existence of appellants' GluR2B receptor, but also the structure and sequence of such a protein."

[53] Paper No. 37, mailed March 18, 1999.

The examiner responds (Answer, page 10) to appellants' argument by citing to Sun's teaching of a cDNA encoding two thirds of human GluR2 as well as the chromosomal location of the corresponding gene in humans. The examiner also states (Answer, bridging paragraph, pages 11-12) "[t]here is no art of record which reports that a human homologue of a known rat neurotransmitter receptor does not exist." This is not the proper foundation for an obviousness rejection.

To be proper, the examiner's rejection requires a reasonable expectation of success in obtaining the human GluR2B receptor of a specified sequence as claimed. The examiner's rejection (Answer, bridging paragraph, pages 6-7) finds that it would have been prima facie obvious to isolate GluR2B from a human cDNA library by probing that library with a rat nucleic acid probe "in a manner that was directly analogous to the one described by Puckett et al."

Sun (abstract) identifies "a second clone, HBGR2, contains approximately two-thirds of the coding region of a receptor homologous to rat brain clone GluR2." Sun teaches (page 1443, Materials and Methods, column 2) that a probe was amplified using two PCR primers derived from GluR1. This probe was then used (Sun, page 1444, bridging paragraph, columns 1-2) for "[h]ybridization screening [of a human brain cDNA library] at high stringency." This screen yielded four positive clones, derived from two different transcripts. The first clone was found to be homologous to rat GluR1, the second clone was found to be homologous to GluR2. Sun, page 1444, bridging paragraph, columns 1-2. Sun localizes the HBGR2-encoding gene on chromosome

[54] Paper No. 36, received January 4, 1999.

4q25-34.3.

At this point we find that under high stringency hybridization conditions, a probe for GluR1 cross-reacts with GluR2. Little more is provided in Sun, other than the "note" at page 1447 which states "[a]fter submission of this manuscript a paper [referring to Puckett] appeared reporting …GluH1. This cDNA shows differences with HBGR1 … in a region corresponding to the alternatively spliced exon identified in the rodent clones by Sommer ['92]… and designated as flip and flop forms of GluR1." So not only is there cross-reactivity between the receptors, there is also the possibility of alternative splicing events.

Puckett, relied upon by the examiner (Answer, page 5) to teach isolation of human GluR1, teaches the use of a reduced stringency hybridization (bridging paragraph pages 7557-558). Furthermore, Puckett also teaches the existence of alternative splicing events (page 7560, column 1), later confirmed by Sun's "note," supra.

The examiner relies upon Heinemann to teach GluR2 (Answer, page 4). We note Heinemann's Example 8 (page 27) which teaches "cDNA clones encoding the GluR2 and GluR3 genes were isolated from an adult rat forebrain library using a low-stringency hybridization screening protocol … and a radiolabeled fragment of the GluR1 cDNA as a probe."

Thus a GluR1 probe cross-reacts with GluR2 and GluR3. Heinemann further teaches that a GluR2 probe cross-reacts with GluR4 and GluR5 (Heinemann, Example 14, page 33).

Here the examiner compares appellants' disclosed sequence with that of the prior art and finds that the amino acid sequence of the human receptor GluR2 is 98% identical to the rat receptor (Answer, page 5). However, without prior knowledge of appellants' sequence, the degree of identity between the claimed human GluR2B and rat GluR2 was unknown. "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." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

Given the degree of cross-reactivity between at least GluR1-5 (as taught by the prior art of record), and the existence of alternative splicing variants amongst these receptors, we can not agree with the examiner (Answer, page 7) that "more than a reasonable expectation that rat GluR2 was structurally and functionally predictive of a homologous human protein and that a cDNA encoding it could be isolated by employing the method of Puckett." The references relied upon, supra, teach that the low stringency hybridization method of Puckett would identify GluR1-5. We do not disagree that given the apparent cross-reactivity of these receptor nucleic acids that an artisan would have certainly identified something. However, based on this record, we do not agree with the examiner that "employing the method of Puckett" a skilled artisan would reasonably have expected to isolate GluR2B as recited in the claim invention.

Therefore, in our opinion, base of this record, the examiner has failed to meet his burden of establishing a prima facie case of obviousness.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Zimmerman Declaration executed July 21, 1997, and the Declarations[55] filed under 37 CFR § 1 .131 of Kamboj (executed August 7, 1997), Nutt (executed June 26, 1997) and Elliott (executed June 26, 1997) relied on by appellants to rebut any such prima facie case.

Accordingly, we reverse the rejection of claims 22, 32 and 34-40 under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett and Sun.

[55] However, we compare the examiner's statement (Answer, page 20) that "[t]he transmission of confidential information does not show a reduction to practice of the claimed isolated DNA," with similar statements made in Appeal Nos.: 1999-1393, 1999-2200, 2000-1778, 2000-1779, and 2000-1780.

Claim 31:

The examiner states (Answer, page 8) "[b]ecause GluR2 was known to be structurally and functionally analogous to the GABA receptor subunit of Cutting et al., an artisan would have found the incorporation of a cDNA encoding that receptor subunit into an expression system like the one described by Cutting et al., and the subsequent preparation of membrane homogenates from the resulting cells to determine the ligand binding characteristics of a receptor composed of human GluR2 in the absence of other human glutamate receptors to have been prima facie obvious in view of this combination of references at the time the instant invention was made."

This rejection based on the combination of Heinemann, Puckett and Sun further in view of Cutting hinges on the fact that it would have been obvious to obtain GluR2B, comprising the amino acid sequence of amino acids 1-863 of SEQ ID NO:2, as recited in the claims. In our opinion, supra, the examiner failed to meet his burden of establishing a prima facie of obviousness, based on the combination of Heinemann, Puckett and Sun. Cutting does not make up for the deficiencies noted above.

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Zimmerman Declaration executed July 21, 1997, and the Declarations filed under 37 CFR § 1.131 of Kamboj (executed August 7, 1997), Nutt (executed June 26, 1997) and Elliott (executed June 26, 1997) relied on by appellants to rebut any such prima facie case.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly, we reverse the rejection of claims 31 and 33 under 35 U.S.C. § 103 as being unpatentable over Heinemann, Puckett and Sun as applied to claims 22, 32 and 34-40 above, and further in view of Cutting.

Summary:

We reverse the examiner's rejection of claims 22, 32, and 34-40 under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett and Sun.

We reverse the examiner's rejection of claims 31 and 33 under 35 U.S.C. § 103 as being unpatentable over Heinemann, Puckett and Sun as applied to claims 22, 32, and 34-40 above and further in view of Cutting.

REVERSED

III. The GLUR3 Subclass:

Appeal No. 1999-2200[56]
Application No. 08/896,063

Claims 1, 16, 23, 42, and 46 are illustrative of the subject matter on appeal and are reproduced below:

1. An isolated polynucleotide which encodes an AMPA-binding human GluR3 having the amino acid sequence of residues 1-866 of SEQ ID NO: 2 or SEQ ID NO: 4.

16. A cellular host having incorporated therein a heterologous polynucleotide which encodes a human GluR3 having the amino acid sequence of residues 1-866 of SEQ ID NO:2 or SEQ ID NO: 4.

23. A membrane preparation derived from a cellular host as defined in claim 16.

42. An isolated polynucleotide as defined in claim 1 which encodes the amino acid sequence of residues 1-866 of SEQ ID NO: 2.

46. An isolated polynucleotide as defined in claim 42, said polynucleotide having the nucleotide sequence 145-2742 of SEQ ID NO: 1.

[56] We recognize appellants' request (Paper No. 28, received May 15, 1999) for oral hearing in this appeal. However, in our review of this appeal we find a hearing is not necessary. 37 CFR § 1.194(c). Accordingly, we make our decision on brief.

GROUNDS OF REJECTION

Claims 23 and 24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Cutting.

Claims 1, 4, 7, 10, 11, 13, 15, 16, 18, 19, 26, and 42-49 are rejected under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett, Sun, Schofield, and Grenningloh.

Claims 23, 24, and 27 are rejected under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett, Sun, Schofield, and Grenningloh as applied to claims 1, 4, 7, 10, 11, 13, 15, 16, 18, 19, 26, and 42-49 above, and further in view of Cutting.

We affirm the rejection under 35 U.S.C. § 102(b), and reverse the rejections under 35 U.S.C. § 103.

The rejection under 35 U.S.C. §102(b):

The examiner states (Answer[57], page 5) that "[n]othing in these claims requires the membrane preparation recited therein to actually contain human GluR3 protein and this limitation does not flow either naturally or inherently from any or all of the limitations recited in the claims.

Appellants respond by arguing (Brief[58], page 7) stating that the membrane preparations are derived from cells transformed with a heterologous polynucleotide which encodes a human GluR3 having a specific amino acid sequence. Therefore, a membrane preparation prepared from such a cell necessarily encodes human

[57] Paper No. 26, mailed March 18, 1999.
[58] Paper No. 25, received January 12, 1999.

GluR3 and is different from the Cutting membrane preparation what does not teach GluR3.

On these facts we agree with the examiner. While the cellular host may be transformed to contain a heterologous polynucleotide encoding human GluR3, there is no requirement in the claims that the claimed membrane preparation actually contain GluR3 protein.

Accordingly, we affirm the examiner's rejection of claims 23 and 24 under 35 U.S.C. § 102(b) as being anticipated by Cutting.[59]

The rejections under 35 U.S.C. §103:

The rejection of claims 1, 4, 7, 10, 11, 13, 15, 16, 18, 19, 26 and 42-49:

The examiner reasons (Answer, page 11) that:

> [T]he combination of the Sun et al., Puckett et al., Schofield et al. and Grenningloh et al. publications provided a reasonable expectation that the sequence and structure of the GluR3 of Heinemann et al. was predictive of a human homologous protein, they would have found it prima facie obvious to have isolated cDNAs encoding human GluR3 by screening a human cDNA library like the one described [by] … Puckett … Schofield …[and] Grenningloh … with a nucleic acid probe corresponding to the rat GluR3 cDNAs of Heinemann et al. in a manner that was directly analogous to those that were employed by each of Puckett et al., Schofield et al. and Grenningloh et al. and then to incorporate that cDNA into a ligand binding assay like that which was described by Heinemann….

The examiner notes (Answer, page 12) that the specification discloses two different nucleotide sequences encoding human GluR3A and GluR3B. However, the examiner finds (Answer, page 12) that since these two different cDNAs were isolated from two different libraries, "[i]t is reasonable to assume that these two cDNA libraries did not come from the same individual." As a result the examiner

[59] Note our statement under 37 CFR § 1.196(c), infra.

concludes (Answer, page 12) that the two sequences "obviously correspond to allelic variations of the same protein and appear to be functionally indistinguishable. Therefore, a DNA encoding either of these variants would have been prima facie obvious in light of the combination of references cited above at the time that the instant invention was made."

Claim 1:

Appellants argue (Brief, pages 10) that the claimed GluR3 sequences differ from those described by the prior art.

The examiner's rejection (Answer, page 11) finds that it would have been prima facie obvious to isolate GluR3 from a human cDNA library by probing that library with a rat nucleic acid probe taught by Heinemann, using methodology of Sun, Puckett, Schofield, and Grenningloh.

Sun teaches (page 1443, Materials and Methods, column 2) that a probe was amplified using two PCR primers derived from GluR1. This probe was then used (Sun, page 1444, bridging paragraph, columns 1-2) for "[h]ybridization screening [of a human brain cDNA library] at high stringency." This screen yielded four positive clones, derived from two different transcripts. The first clone was found to be homologous to rat GluR1, the second clone was found to be homologous to GluR2. Sun, page 1444, bridging paragraph, columns 1-2.

At this point we find that under high stringency hybridization conditions, a probe for GluR1 cross-reacts with GluR2. Little more is provided in Sun, other than the "note" at page 1447 which states "[a]fter submission of this manuscript a paper [referring to Puckett] appeared reporting …GluH1. This cDNA shows differences with HBGR1 … in a region corresponding to the alternatively spliced

exon identified in the rodent clones by Sommer ['92] … and designated as flip and flop forms of GluR1." So not only is there cross-reactivity between the receptors, there is also the possibility of alternative splicing events.

Puckett relied upon by the examiner (Answer, page 11) to teach isolation of human GluR1, teaches the use of a reduced stringency hybridization (bridging paragraph pages 7557-558). Furthermore, Puckett also teaches the existence of alternative splicing events (page 7560, column 1), later confirmed by Sun's "note," supra.

The examiner relies upon Heinemann to teach GluR3 (Answer, page 4). We note Heinemann's Example 8 (page 27) which teaches "cDNA clones encoding the GluR2 and GluR3 genes were isolated from an adult rat forebrain library using a low-stringency hybridization screening protocol … and a radiolabeled fragment of the GluR1 cDNA as a probe."

Thus a GluR1 probe cross-reacts with GluR2 and GluR3. Thus, at the time this invention was made, following the methodology set forth by the examiner one would have expected a probe based on Heinemann's GluR3 to cross-react with at least GluR1-2.

It is unclear from this record where the examiner finds an objective basis to apply Grenningloh and Schofield, neither of which teaches a glutamate receptor. Before, a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

The examiner's states (Answer, bridging paragraph, pages 10-11) that:

> [T]he … publications are being relied upon in combination because they show that it was known in the art prior to the making of the instant invention that the sequences and structures of those proteins that serve as the subunits of ligand-gated ion channels (a.k.a. ionotropic receptors) from one mammal were known to be predictive of the structures and functions of homologous proteins from other mammals and that an artisan had more than a reasonable expectation the structure and function of the GluR3 subunit of Heinemann et al. to be predictive of a homologous human protein.

However, given the teachings of Sun, Puckett and Heinemann, supra, of cross-reactivity at the nucleic acid level we are of the opinion that a person of ordinary skill in the art would not have a reasonable expectation of success in isolating the GluR3A or GluR3B receptor. Furthermore, none of these references teach the existence of two forms of the GluR3 receptor, GluR3A and 3B. The initial burden of establishing reasons for unpatentability rests on the examiner. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Furthermore, to establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

We do not agree with the examiner's conclusion (Answer, page 12) that due to the library in which they were isolated the GluR3A and GluR3B sequences "obviously correspond to allelic variations of the same protein and appear to be functionally indistinguishable." On this record, in the absence of appellants' disclosure a person of ordinary skill in the art would not have known that GluR3a and

GluR3B existed. We remind the examiner that "[t]he Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because it may doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis." In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968).

Here, we agree with the appellants (Brief, pages 14-18) that there is no teaching or suggestion in the applied prior art of the GluR3A receptor having the amino acid sequence of residues 1-866 of SEQ ID NO:2 or the GluR3B receptor having amino acid sequence of residues 1-866 of SEQ ID NO:4 as required by the claim. In re Ochiai, 71 F.3d 1565, 1570, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). We also do not find that there was a reasonable expectation that one could have obtained such a receptor sequence required to perform the claimed methods. In re O'Farrell, 858 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)(obviousness also requires a "reasonable expectation of success.")

Claim 46:

Appellants argue (Brief, page 35) "[t]he [e]xaminer also has not explained why the combination of documents would have suggested an assay using specific DNA sequences as recited in claims 46-49." [emphasis removed].

In response the examiner states (Answer, bridging paragraph, pages 29-30:

> Those nucleotide sequences are the inherent properties of cDNAs which existed in the prior art. The prior art of record provided compositions containing those cDNAs in the form of … cDNA libraries…. It further provided analogous compositions and the means and motivation to isolate from those libraries a cDNA of the instant invention. Because a chemical compound and all of its properties are inseparable, and the sequence of a cDNA encoding human GluR3 was an inherent property of that compound as it existed prior to being isolated by [a]ppellant, that limitation was fairly taught by the combination of references cited above.

We note the examiner's use of "GluR3" instead of either GluR3A or GluR3B. This is apparently because the examiner's combination of references fails to teach GluR3A (SEQ ID NO:1) or GluR3B (SEQ ID NO:3). See specification, page 3, for definition of SEQ ID NOs: 1 & 3 as GluR3A and GluR3B respectively. Here, the examiner has failed to meet his burden of establishing a prima facie case of obviousness for either of the specifically claimed sequences. We see no teaching in the combination of prior art relied upon by the examiner which teaches, suggests or renders the specifically claimed sequences prima facie obvious. It is the examiner who has the initial burden of establishing unpatentability. In re Oetiker, 977 F.2d 1443, 1446,
24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Conclusions of obviousness must be based upon facts, not generality. In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968); In re Freed, 425 F.2d 785, 788, 165 USPQ 570, 571 (CCPA 1970).

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Zimmerman Declaration

executed July 21, 1997, and the Declarations[60] filed under 37 CFR §1.131 of Kamboj (executed August 7, 1997), Nutt (executed June 26, 1997) and Elliott (executed June 26, 1997) relied on by appellants to rebut any such prima facie case.

Accordingly, we reverse the examiner's rejection of claims 1, 4, 7, 10, 11, 13, 15, 16, 18, 19, 26, and 42-49 under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett, Sun, Schofield, and Grenningloh.

The rejection of claims 23, 24 and 27:

Claim 23:

Cutting fails to make up the deficiencies identified supra for the combination of Heinemann in view of Puckett, Sun, Schofield, and Grenningloh.

Therefore the examiner has failed to meet his burden of establishing a prima facie case of obviousness for obtaining the claimed membrane preparation.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

[60] However, we compare the examiner's statement (Answer, page 30) that "[t]he transmission of confidential information does not show a reduction to practice of the claimed isolated DNA," with similar statements made in Appeal Nos.: 1999-1393, 1999-2118, 1999-2200, 2000-1778, 2000-1779, and 2000-1780.

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Zimmerman Declaration executed July 21, 1997, and the Declarations[61] filed under 37 CFR § 1.131 of Kamboj (executed August 7, 1997), Nutt (executed June 26, 1997) and Elliott (executed June 26, 1997) relied on by appellants to rebut any such prima facie case.

Accordingly, we reverse the examiner's rejection of claims 23, 24 and 27 under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett, Sun, Schofield and Grenningloh as applied to claims 1, 4, 7, 10, 11, 13, 15, 16, 18, 19, 26 and 42-49 above, and further in view of Cutting.

Statement under 37 CFR § 1.196(c):

It appears to us that the rejection of claims 23 and 24 under 35 U.S.C. § 102(b) as being anticipated by Cutting may be over come by adding a phrase to the claim that requires GluR3's presence in the membrane. We note of interest, a phrase from Appeal No. 2000-1779, Application No. 08/473,204, claim 17 "a membrane preparation that contains human GluR4B protein."

Time Period for Response for Appeal No. 1999-2200:

This opinion in Appeal No. 1999-2200 contains a statement pursuant to 37 CFR § 1.196(c) has been made in this decision. 37 CFR § 1.196(c) provides:

> Should the decision of the Board of Patent Appeals and Interferences include an explicit statement that a claims may be allowd in amended form, appellants shall have the right to amend in conformity with such statement which shall be binding upon the examiner in the absence of new references or grounds of rejection.

[61] However, we compare the examiner's statement (Answer, page 30) that "[t]he transmission of confidential information does not show a reduction to practice of the claimed isolated DNA," with similar statements made in Appeal Nos.: 1999-1393, 1999-2118, 1999-2200, 2000-1778, 2000-1779, and 2000-1780.

A time period in which appellants may file an amendment for the purpose stated in § 1.196(c) is hereby set to expire TWO MONTHS FROM THE DATE OF THIS DECISION.

Summary:

We affirm the examiner's rejection of claims 23 and 24 under 35 U.S.C. § 102(b) as being anticipated by Cutting.

We reverse the examiner's rejection of claims 1, 4, 7, 10, 11, 13, 15, 16, 18, 19, 26, and 42-49 are rejected under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett, Sun, Schofield and Grenningloh.

We reverse the examiner's rejection of claims 23, 24 and 27 are rejected under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett, Sun, Schofield and Grenningloh as applied to claims 1, 4, 7, 10, 11, 13, 15, 16, 18, 19, 26, and 42-49 above, and further in view of Cutting.

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

AFFIRMED-IN-PART, 37 CFR § 1.196(c)

Appeal No. 2000-1778
Application No. 08/257,029

Claims 28, 43, 44 and 49 are illustrative of the subject matter on appeal and are reproduced below:

28. A method of assaying a substance for binding to human GluR3, which comprises the steps of:
    incubating a cellular host, or a membrane preparation derived from said cellular host, with labeled GluR3 ligand to form a ligand/receptor complex, the cellular host having incorporated expressibly therein a heterologous polynucleotide that encodes a human GluR3 selected from the group consisting of human GluR3A and human GluR3B,
        removing unbound ligand, and
        measuring the amount of ligand displaced from or remaining in the receptor/ligand complex.

43. A method as claimed in claim 28, wherein the cellular host has incorporated expressibly therein a heterologous polynucleotide that encodes human GluR3 selected from the group consisting of human GluR3A and human GluR3B.

44. A method as claimed in claim 43, wherein the cellular host has incorporated expressibly therein a heterologous polynucleotide that encodes human GluR3A having the sequence of SEQ ID NO:2.

49. A method as claimed in claim 28, wherein the heterologous polynucleotide is plasmid pBS/humGluR3A (ATCC 75218).

GROUNDS OF REJECTION

Claims 28, 43-45, and 49-52 are rejected under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett and Sun.

We reverse.

The rejection under 35 U.S.C. § 103:

The examiner states (Answer[62], bridging paragraph, pages 7-8) that:

> The isolation of a cDNA encoding the human counterpart of the rat GluR3 subunit that was described in the Heinemann et al. publication by probing the cDNA library of Sun et al. or Puckett et al., each of which was constructed from mRNA isolated from human brain, with a nucleic acid probe encoding all or part of rat GluR3 in a manner that was directly analogous to the method described by Puckett et al. to facilitate the recombinant expression and characterization of the encoded product in the absence of other human glutamate receptor subunits for those reasons that were expressly given by Sun et al. would have been prima facie obvious to an artisan of ordinary skill in the art of molecular biology at the time that the instant invention was made.

The examiner further states (Answer, bridging paragraph, pages 8-9) that since the GluR3A and GluR3B sequences were isolated from different cDNA libraries "they obviously correspond to allelic variations of the same protein and appear to be functionally indistinguishable."

Claim 28:

Appellants argue (Brief, pages 12-17) that the claimed GluR3 sequences differ from those described by the prior art.

[62] Paper No. 26, mailed February 5, 1999.

The examiner's rejection (Answer, bridging paragraph, pages 7-8) finds that it would have been prima facie obvious to isolate GluR3 from a human cDNA library by probing that library with a rat nucleic acid probe taught by Heinemann, using methodology described by Puckett. The examiner, citing In re Pleuddemann, 910 F.2d 823, 15 USPQ2d 1738 (Fed. Cir. 1990), states (Answer, page 4) that "[t]he novelty of the instant invention is in the use of a novel nucleic acid in that method and not in the method itself and, therefore, the patentability of the claimed method is dependent upon the patentability of the nucleic acid employed therein."

Sun teaches (page 1443, Materials and Methods, column 2) that a probe was amplified using two PCR primers derived from GluR1. This probe was then used (Sun, page 1444, column 1) for "[h]ybridization screening [of a human brain cDNA library] at high stringency." This screen yielded four positive clones, derived from two different transcripts. The first clone was found to be homologous to rat GluR1, the second clone was found to be homologous to GluR2. Sun, page 1444, bridging paragraph, columns 1-2.

At this point we find that under high stringency hybridization conditions, a probe for GluR1 cross-reacts with GluR2. Little more is provided in Sun, other than the "note" at page 1447 which states "[a]fter submission of this manuscript, a paper [referring to Puckett] appeared reporting …GluH1. This cDNA shows differences with HBGR1 … in a region corresponding to the alternatively spliced exon identified in the rodent clones by Sommer ['92] … and designated as flip and flop forms of GluR1." So not only is there cross-reactivity between the receptors, there is also the possibility of alternative splicing events.

Puckett relied upon by the examiner (Answer, page 11) to teach isolation of human GluR1, teaches the use of a reduced stringency hybridization (bridging paragraph pages 7557-558). Furthermore, Puckett also teaches the existence of alternative splicing events (page 7560, column 1), later confirmed by Sun's "note," supra.

The examiner relies upon Heinemann to teach GluR3 (Answer, page 4). We note Heinemann's Example 8 (page 27) which teaches "cDNA clones encoding the GluR2 and GluR3 genes were isolated from an adult rat forebrain library using a low-stringency hybridization screening protocol … and a radiolabeled fragment of the GluR1 cDNA as probe."

Thus a GluR1 probe cross-reacts with GluR2 and GluR3. Thus, at the time this invention was made, following the methodology set forth by the examiner one would have expected a probe based on Heinemann's GluR3 to cross-react with at least GluR1-2.

However, given the teachings of Sun, Puckett and Heinemann, supra, of cross-reactivity at the nucleic acid level we are of the opinion that a person of ordinary skill in the art would not have a reasonable expectation of success in isolating the GluR3A or GluR3B receptor. Furthermore, none of these references teach the existence of two forms of the GluR3 receptor, GluR3A and 3B.

We do not agree with the examiner's conclusion (Answer, bridging paragraph, pages 8-9) that due to the library in which they were isolated the GluR3A and GluR3B sequences "obviously correspond to allelic variations of the same protein and appear to be functionally indistinguishable." On this record, in the

absence of appellants' disclosure a person of ordinary skill in the art would not have known that GluR3A and GluR3B existed. We remind the examiner that "[t]he Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because it may doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis." In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968).

Here, we agree with the appellants (Brief, pages 8-13) that there is no teaching or suggestion in the applied prior art of the GluR3A receptor having the amino acid sequence of residues 1-866 of SEQ ID NO:2 or the GluR3B receptor having amino acid sequence of residues 1-866 of SEQ ID NO:4 as required by the claim. In re Ochiai, 71 F.3d 1565, 1570, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). We also do not find that there was a reasonable expectation that one could have obtained such a receptor sequence required to perform the claimed methods. In re O'Farrell, 858 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)(obviousness also requires a "reasonable expectation of success").

Claims 44 and 49:

Appellants state (Brief, bridging paragraph, pages 23-24) that "[t]he sequences recited in appellants' claims 44 and 45, and more particularly plasmids including these specific sequences, as claimed in claims 49 and 50, would not have been structurally obvious in light of the combination of references."

In response the examiner states (Answer, page 19) that:

> The simple fact that the nucleotide sequence of the cDNAs encoding the rat glutamate receptor subunit GluR3 of Heinemann et al. is different from the sequence of the cDNAs of the instant invention does not defeat the instant rejection since the prior art of record provided a structurally similar composition and the motivation to isolate any analogous compound from any human brain cDNA library of the prior art. The fact that this property differs slightly and inconsequentially from individual to individual does not support patentability since these difference[s] are the innate differences between naturally occurring compounds and do not constitute an inventive contribution by [a]pplicant.

By suggesting that "this property differs slightly and inconsequentially from individual to individual does not support patentability since these difference[s] are the innate differences between naturally occurring compounds and do not constitute an inventive contribution" the examiner is essentially adopting a per se rule. We remind the examiner that there are no per se rules of obviousness. In re Ochiai, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995). Every case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts. In re Jones, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

Here again there is no teaching or suggestion in the applied prior art of the GluR3A receptor having the amino acid sequence of residues 1-866 of SEQ ID

NO:2 or the GluR3B receptor having amino acid sequence of residues 1-866 of SEQ ID NO:4 as required by the claim. In re Ochiai, 71 F.3d 1565, 1570, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). We also do not find that there was a reasonable expectation that one could have obtained such a receptor sequence required to perform the claimed methods. In re O'Farrell, 858 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)(obviousness also requires a "reasonable expectation of success").

The examiner has the burden of supplying a factual basis to support his obviousness rejection. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). We also remind the examiner that conclusions of obviousness must be based upon facts, not generality. In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968); In re Freed, 425 F.2d 785, 788, 165 USPQ 570, 571 (CCPA 1970).

In our opinion, on these facts, the examiner failed to meet his burden of establishing a prima facie case of obviousness.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Zimmerman Declaration

executed July 21, 1997, and the Declarations[63] filed under 37 CFR § 1.131 of Kamboj (executed August 7, 1997), Nutt (executed June 26, 1997) and Elliott (executed June 26, 1997) relied on by appellants to rebut any such prima facie case.

Accordingly, we reverse the rejection of claims 28, 43-45, and 49-52 under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett and Sun.

Other Matters:

The examiner and appellants should review claims 28 and 43 to determine if claim 43 further limits claim 28. See 35 U.S.C. § 112, fourth paragraph. See also MPEP 706.03(k).

Summary:

We reverse the examiner's rejection of claims 28, 43-45, and 49-52 under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett and Sun.

REVERSED

[63] However, we compare the examiner's statement (Answer, page 20) that "[t]he transmission of confidential information does not show a reduction to practice of the claimed isolated DNA," with similar statements made in Appeal Nos.: 1999-1393, 1999-2118, 1999-2200, 2000-1779, and 2000-1780.

IV. The GLUR4 Subclass:

Appeal No. 2000-1779
Application No. 08/473,204

Claims 17 and 31[64] are illustrative of the subject matter on appeal and are reproduced below:

17. A membrane preparation that contains human GluR4B protein, said membrane preparation being derived from a cellular host having incorporated therein a heterologous polynucleotide comprising a region that encodes human GluR4B.

31. A membrane preparation as claimed in claim 17, wherein the human GluR4B protein comprises amino acid residues 1-881 of SEQ-ID NO:2.

GROUNDS OF REJECTION[65]

Claims[66] 17, 19 and 31 are rejected under 35 U.S.C. § 103 as being unpatentable over the combination of McNamara and Sommer '90.

We affirm the rejection of claims 17 and 19 under 35 U.S.C. § 103. We reverse the rejection of claim 31 under 35 U.S.C. § 103.

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[64] We note that claim 31 was incorrectly presented in the appendix of Appellants' Brief (Paper No. 16, received November 4, 1998). Claim 31 was amended in Appellants' response received August 13, 1997 (Paper No. 7). Claim 31 is correctly reproduced herein.

[65] We note the examiner's reference at pages 7-9 of the Answer to Puckett et al. "Molecular cloning and chromosomal localization of one of the human glutamate receptor genes," Proceedings of the National Academy of Science, USA, Vol. 88, pp. 7557-561 (1991), and to Sun et al. "Molecular cloning, chromosomal mapping, and functional expression of human brain glutamate receptors," Proceedings of the National Academy of Science, USA, Vol. 89, pp. 1443-447 (1992). However, we remind the examiner that "[w]here a reference is relied on to support a rejection, whether or not in a 'minor capacity,' there would appear to be no excuse for not positively including the reference in the statement of the rejection. In re Hoch, 428 F.2d 1341, 1342 n.3, 166 USPQ 406, 407 n.3 (CCPA 1970).

[66] We note the following typographical error in the examiner's statement of the rejection at page 3 of the Answer, "[c]laims 17 to 19 and 31," should read --[c]laims

The rejections under 35 U.S.C. § 103

The examiner reasons (Answer[67], page 4) that:

> The McNamara et al. publication, taken alone, clearly placed an isolated cDNA encoding a human GluR4 protein in the hands of an artisan of ordinary skill at the time of the instant invention. The isolation of that cDNA only requires an artisan to screen a cDNA library produced from human brain mRNA with a nucleic acid probe encoding rat GluR4 in the same manner that McNamara et al. employed to screen the human genomic library described therein.

In the bridging paragraph of pages 4-5 of the Answer, the examiner states:

> To have incorporated that cDNA into an expression vector and host cell to obtain the expression and quantitative production of human GluR4 and to permit the characterization of that protein at the molecular level by employing those methods that were old and well known in the art would have been prima facie obvious in view of this [McNamara] reference. Further, the production of a membrane preparation containing such a protein from a host cell to permit the evaluation of the binding characteristics of a receptor protein was a practice that was also old and well known at the time that the instant invention was made.

In the bridging paragraph of pages 5-6 of the Answer, the examiner relies upon Sommer '90 for the teaching that GluR1-A, -B, -C, and –D exist in one of two (flip and flop) sequence versions.

Characterizing GluR4B as GluR-D the examiner concludes at page 6 of the Answer, that:

> Because McNamara disclosed that humans have a GluR-D gene, as well as the location of that gene and

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17, 19 and 31 --. These three claims are the only claims pending and on appeal in this application.

[67] Paper No. 17, mailed January 22, 1999.

> the fact that a nucleic acid encoding human GluR-D could be detected by employing a nucleic acid probe encoding all or part of rat GluR-D, that artisan had more than a reasonable expectation of successfully isolating cDNAs encoding human flip and flop GluR-Ds.

The examiner's position is that once isolated by the combined teachings of McNamara and Sommer '90, the GluR4B cDNA could be placed in a suitable vector for expression in a host cell from which a membrane preparation as claimed could be derived. However, the examiner's rejection hinges on the rationale that it would be obvious to obtain a GluR4B cDNA.

With regard to the examiner's position, we note that the instant application is a divisional application of Serial No. 08/259,164, now United States Patent No. 5,643,785 ('785). It appears that the examiner's rejection of claim 31 in the present application under 35 U.S.C. § 103 is inconsistent with the determination that claims 1, 4 and 8 of '785 are patentable. Claims 1, 4 and 8 of the '785 patent read as follows:

1. An isolated polynucleotide that encodes an AMPA-binding human GluR4B receptor having the sequence of amino acid residues 1-881 of SEQ ID NO:2.

4. A recombinant DNA vector comprising a polynucleotide that encodes an AMPA-binding human GluR4B receptor having the sequence of amino acid residues 1-881 of SEQ ID NO:2.

8. A mammalian cell genetically engineered to produce GluR4B receptor, said cell containing a heterologous polynucleotide that encodes an AMPA-binding human GluR4B receptor having the sequence of amino acid residues 1-881 of SEQ ID NO:2.

In addition, both references (McNamara and Sommer '90) relied upon in the present application to support the rejection under 35 U.S.C. § 103 are cited on the face of the '785 patent as considered.

While the examiner may issue a rejection if appropriate under these circumstances, a rejection using the rationale set forth above would appear to require the signature of the Group Director. Compare MPEP ' 2307.02 (7th ed., July 1998). We note the Group Director did not sign the examiner's action.

Generally, appeals on these facts are remanded to provide the examiner an opportunity to consider the issued patent and determine its effect, if any, on the issues raised under 35 U.S.C. § 103. However, after considering the facts in this case we believe the better course of action is to move forward with a decision on the merits of this appeal.

The initial burden of establishing reasons for unpatentability rests on the examiner. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). To establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. Furthermore, the prior art must teach of suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

On this record, the examiner applies McNamara for the teaching of the chromosomal localization of a human GluR4 receptor gene (Figure 3, and discussion bridging paragraph pages 2560-561). According to McNamara, (page

2555, Materials and Methods) a human placental DNA library was screened for GluR1-4 by hybridization to radiolabeled probes of rat GluR1-4 cDNA. McNamara (page 2556, Results) reports the isolation of cosmid clones containing portions of the putative human GluR genes by hybridization under stringent conditions with the homologous cDNA obtained from rat, and that "[u]nder these conditions, the cosmid clones hybridized to radiolabeled cDNA of mainly one GluR cDNA." McNamara (page 2556, Results) further reports that "[i]n every instance, the homology of the human GluR sequence was higher with its respective rat cDNA than with rat cDNAs encoding other GluRs." This data is illustrated in Table 1 (page 2557). McNamara states (page 2557, Discussion) "[t]he results of selective hybridization and partial sequence analysis support the conclusion that the genomic clones isolated represent human homologs corresponding to rat GluR1-4." McNamara does not teach a nucleotide or amino acid sequence of GluR4. Additionally, McNamara does not teach a GluR4B receptor.

However, Sommer '90 is cited by the examiner for teaching flip and flop forms of GluRA-D. We note that McNamara (page 2555, column 2) recognizes a correspondence between the nomenclature of human GluR1-4 and rat GluRA-D. Thus rat GluRD corresponds to human GluR4. We also note that Sommer '90 teach (Figure 1, page 1581) the "complete nucleotide sequences encoding the flop-containing polypeptides are deposited at EMBL/GenBank under accession numbers … M36421 (GluR-D) and the corresponding flip versions under … M38063 (GluR-D)."

Appellants argue (Brief[68], page 8) that "[i]t is entirely possible, given the lack of sequence information or functional characterization of the alleged GluR4 gene, that McNamara has isolated a partial clone of a different GluR gene that is homologous to the rat GluR4 in the short stretch sequenced." Indeed, McNamara recognizes this (page 2556, column 2) "[t]hese homologies are based upon the relatively short DNA sequences as specified in the notes to Table 1." However, McNamara (page 2556, column 2) points out that the mismatches identified are conservative since the identity of the amino acid sequence was 100% for GluR4, that identical mismatches were identified by Puckett for GluR1 and that in every instance the homology of the human GluR sequence was higher with its respective rat cDNA than with rat cDNAs encoding other GluRs. McNamara concludes (page 2556, column 2) "[t]ogether, these data support the conclusion that these cosmid clones contain the likely human homologs of rat GluR1-4."

Claims 17 and 19:

The examiner concludes (Answer, page 6) that:

> Because McNamara disclosed that humans have a GluR-D gene, as well as the location of that gene and the fact that a nucleic acid encoding human GluR-D could be detected by employing a nucleic acid probe encoding all or part of rat GluR-D, that artisan had more than a reasonable expectation of successfully isolating cDNAs encoding human flip and flop GluR-Ds.

Given the fact that Sommer teaches the complete nucleotide sequence encoding GluR-D flop and flip are available at EMBL/GenBank under accession numbers M36421 and M38063 respectively, we agree with the examiner that a

[68] Paper No. 16, received November 4, 1998.

reasonable expectation of success existed based on the combined teachings of McNamara and Sommer to obtain a cDNA encoding GluR4B.

The examiner notes (Answer, bridging paragraph, pages 17-18) that Sommer et al. teach cultured mammalian cells engineered with GluR genes for electrophysiological characterization (Sommer, column 1, page 1581, and Sommer, reference 8). We therefore, agree with the examiner's conclusion (Answer, page 18) that:

> [A] membrane preparation containing human GluR4 would have been obvious since the polynucleotide encoding human GluR4B was obvious, advantages of expressing a heterologous GluR receptor in a cell for pharmacological analysis of the receptor were known, and it was routine to use membrane preparation as well as whole cells for such pharmacological investigations to analyze properties of drugs with clinical potential.

Appellants provide the Kamboj Declaration, executed August 7, 1997, under 37 CFR § 1.131 and state (Brief, page 12) "applicants have made of record Rule 131 declaration by inventors Kamboj, Nutt and Elliott." However, as the examiner notes (Answer, page 13):

> [T]he declaration under 37 CFR [§] 1.131 must be executed by all the inventors of the claimed invention, which has not been done. Appellants say at the beginning of section 4 on page 15 of the brief that declarations signed by inventors Nutt and Elliott are attached to the brief, but no such declarations accompanied the appeal brief.

Since the declaration filed under 37 CFR §1.131 was not properly executed, we will not address the merits of the declaration[69].

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[69] However, we note the examiner's statement (Answer, page 13) "[t]he Rule 1.131 declaration submitted by [a]ppellants would only be sufficient to effectively establish reduction to practice prior to McNamara for the teaching that there is conservation

Accordingly, we affirm the rejection of claims 17 and 19 under 35 U.S.C. §103 over the combination of McNamara and Sommer.[70]

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between the human GluR1-3 compared to rat GluR1-5 as well as human EAA1a and EAA2a receptors, but no additional teachings."

[70] We recognized that our decision in this appeal may appear to be in conflict with our decisions in related Appeal Nos.: 1999-1393 (e.g. claim 1, drawn to an isolated polynucleotide that encodes human GluR2B) and 2000-1778 (e.g. claim 28, drawn to a method of assaying, wherein a cellular host has incorporated therein a polynucleotide encoding human GluR3A or GluR3B). Both the related appeals and the instant appeal include claims drawn to, or including limitations to, polynucleotides generically. To distinguish these appeals, we note that "[t]here must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from applicant's disclosure." In re Dow Chem. Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988), citing, Interconnect Planning Corp. v. Feil, 744 F.2d 1123, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985). In the instant appeal the examiner bases the rejection on the combination of McNamara and Sommer '90. McNamara, supra, teaches the identification of GluR4 by hybridizing a human cDNA library with a rat GluR4 probe. McNamara further teaches the chromosomal location of human GluR4. In addition, McNamara recognizes (Table 1, page 2557) the cross-reactivity among the GluR nucleic acids, but notes "that the nucleotide homology is highest with the respective rat cDNA predicted by hybridization results." Sommer, relied upon by this examiner, teaches the nucleic acid sequences for both the flip and flop forms of rat GluR4 are available from EMBL/GenBank. In contrast, in both Appeal Nos.: 1999-1393 (GluR2B) and 2000-1778 (GluR3A and GluR3B) the examiner relies on the combination of Heinemann in view of Puckett and Sun. Sun, supra, teaches the chromosomal location of GluR2. Sun further teaches the identification of GluR2 using a GluR1 probe. While both Sun and Puckett recognize flip and flop forms exist, in contrast to the instant appeal, neither teach a sequence for either form of GluR2. With regard to GluR3, none of the applied prior art suggests that it exists in humans, and no chromosomal location is identified. Further, the combination of Heinemann, Puckett and Sun, unlike McNamara do not resolve the issue of cross-hybridization. On these records, in our opinion, in contrast to the factual evidence provided in Appeal Nos. 1999-1393 and 2000-1778, the factual evidence presented in Appeal No. 2000-1779 provides one of ordinary skill in the art a reasonable expectation of success and suggests to one of ordinary skill in the art the desirability of obtaining an isolated a polynucleotide encoding GluR4B upon which a membrane preparation as claimed can be obtained, as explained by the examiner, supra. Compare Ex parte Goldgaber, 41 USPQ2d 1172 (Bd. Pat. App. & Int. 1995).

Claim 31:

We note the examiner's statement (Answer, page 8) that "[t]he disclosure of the sequence of human GluR4B as amino acids 1-881 of SEQ ID NO:2 is the recitation of an inherent property of a protein that was known to exist and does not make that compound unobvious."

In response, appellants cite (Reply Brief[71], page 1) In re Spormann, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966) for the position that "[t]hat which may be inherent is not necessarily known …. Obviousness cannot be predicated on what is unknown." We agree.

There is no suggestion or reasonable expectation in the combination of prior art relied upon by the examiner that a GluR4B comprising amino acid residues 1-881 of SEQ-ID NO:2 would have been obtained. Therefore, in our opinion, the examiner failed to meet her burden of establishing a prima facie case of obviousness.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly, we reverse the rejection of claim 31 under 35 U.S.C. § 103 over the combination of McNamara and Sommer.

Summary:

We affirm the rejection of claims 17 and 19 under 35 U.S.C. § 103 as being unpatentable over the combination of McNamara and Sommer '90.

We reverse the examiner's rejection of claim 31 under 35 U.S.C. § 103 as being unpatentable over the combination of McNamara and Sommer '90.

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

[71] Paper No. 18, received March 22, 1999.

Appeal No. 2000-1780
Application No. 08/403,663

Claim 22[72] is illustrative of the subject matter on appeal and is reproduced below:

> 22. A method of assaying interaction between a test ligand and a receptor of the human central nervous system, which comprises incubating the test ligand with a cellular host or with membrane preparation derived from said cellular host, said cellular host having incorporated expressibly therein a heterologous polynucleotide encoding the human GluR4B receptor having the amino acid sequence of residues 1-881 of SEQ ID NO: 2 or an AMPA-binding fragment of said GluR4B receptor having the amino acid sequence that is a fragment of the amino acid sequence of residues 1-881 of SEQ ID NO: 2, and determining the extent of interaction between said GluR4B receptor or said fragment and the test ligand.

GROUNDS OF REJECTION[73]

Claims 22-23 and 34-38 are rejected under 35 U.S.C. § 103 as being unpatentable over Keinanen in view of Sommer '90 and McNamara.

We reverse.

[72] We note that claim 22 was incorrectly presented in the appendix of Appellants' Brief (Paper No. 20, received November 3, 1998). Claim 22 was amended in appellants' amendment received May 11, 1995 (Paper No. 6). Claim 22 is correctly reproduced herein.

[73] We note the examiner's reference at pages 7 and 10 of the Answer to Puckett et al. "Molecular cloning and chromosomal localization of one of the human glutamate receptor genes," Proceedings of the National Academy of Science, USA, Vol. 88, pp. 7557-561 (1991), and to Sun et al. "Molecular cloning, chromosomal mapping, and functional expression of human brain glutamate receptors," Proceedings of the National Academy of Science, USA, Vol. 89, pp. 1443-447 (1992). However, we remind the examiner that "[w]here a reference is relied on to support a rejection, whether or not in a 'minor capacity,' there would appear to be no excuse for not positively including the reference in the statement of the rejection. In re Hoch, 428 F.2d 1341, 1342 n.3, 166 USPQ 406, 407 n.3 (CCPA 1970).

The rejection under 35 U.S.C. § 103:

The examiner explains (Answer[74], page 4) that while Keinanen do not teach using human GluR4B, the reference teaches a method of assaying interactions using a cellular host, or membrane derived from a cellular host, that expresses the rat homolog of human GluR4B. The examiner relies upon Sommer '90 for the teaching, inter alia, that "GluR exists as a flip or flop (A or B) form." See Answer, page 5. The examiner explains at page 6 of the Answer, that McNamara obtained a cosmid clone containing a portion of human GluR4, and that the nucleic acid of this GluR4 was 93% identical to the rat GluR4B.

At page 8 of the Answer, the examiner concludes that:

> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the assay of Keinanen et al. using a human cDNA for heterologous GluR4B receptor expression obtained by using the DNA of McNamara et al. as a radiolabeled probe to screen a commercially available human brain or placental cDNA library and subcloning the isolated library clone into the pCDM8 plasmid and transfecting a eukaryotic cell of heterologous receptor expression by the screening, subcloning, and transfection methods taught by Keinanen et al.

The examiner's rejection hinges on the rationale that it would be obvious to obtain the human GluR4B cDNA, and once obtained, to introduce the cDNA into a system whereby the claimed assay could be performed. It appears to us that the examiner's rejection of the claims in the present application under 35 U.S.C. § 103 is inconsistent with the determination that claims 1, 4 and 8 of United States

[74] Paper No. 21, mailed January 22, 1999.

Patent No. 5,643,785 ('785) are patentable[75]. Claims 1, 4 and 8 of the '785 patent read as follows:

1. An isolated polynucleotide that encodes an AMPA-binding human GluR4B receptor having the sequence of amino acid residues 1-881 of SEQ ID NO:2.

4. A recombinant DNA vector comprising a polynucleotide that encodes an AMPA-binding human GluR4B receptor having the sequence of amino acid residues 1-881 of SEQ ID NO:2.

8. A mammalian cell genetically engineered to produce GluR4B receptor, said cell containing a heterologous polynucleotide that encodes an AMPA-binding human GluR4B receptor having the sequence of amino acid residues 1-881 of SEQ ID NO:2.

In addition, the Keinanen, McNamara and Sommer '90 references relied upon in the present application to support the rejection under 35 U.S.C. § 103 are cited on the face of the '785 patent as considered.

While the examiner may issue a rejection if appropriate under these circumstances, a rejection using the rationale set forth above would appear to require the signature of the Group Director. Compare MPEP ' 2307.02 (7th ed., July 1998). We note the Group Director did not sign the examiner's action.

Generally, appeals on these facts are remanded to provide the examiner an opportunity to consider the issued patent and determine its effect, if any, on the issues raised under 35 U.S.C. § 103. However, after considering the facts in this

[75] We note that the instant application and Serial No. 08/259,164, now the '785 patent share the same parent application. The present application is a continuation of Serial No. 08/091,440, which is a divisional of Serial No. 07/924,553. '785 issued from application Serial No. 08/259,164 which is a continuation of Serial No. 07/924,553.

case we believe the better course of action is to move forward with a decision on the merits of this appeal.

The initial burden of establishing reasons for unpatentability rests on the examiner. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). To establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. Furthermore, the prior art must teach of suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Claims 22 and 35:

Appellants argue (Brief[76], page 8) "[b]ased on the minimal teaching, applicants assert that an assay using a cellular host or membrane preparation which expresses a polynucleotide that specifically encodes a receptor having the amino acid sequence of residues 1-881 of SEQ ID NO:2 is clearly not suggested by the combination of references." We agree.

The examiner emphasizes (Answer, pages 5-7) the sequence homology between Keinanen's rat GluR4B and the claimed GluR4B. However, we find no teaching or suggestion in the combination of prior art relied upon by the examiner that a human GluR4B having the amino acid sequence of residues 1-881 of SEQ ID NO:2 or a fragment thereof can be obtained with a reasonable expectation of success.

[76] Paper No. 20, received November 3, 1998.

Without a cDNA having the claimed sequence, a method of assaying as claimed can not be reasonably expected. Therefore, in our opinion, the examiner failed to meet her burden of establishing a prima facie case of obviousness.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Kamboj Declaration[77], executed August 7, 1997, under 37 CFR § 1.131, relied on by appellants to rebut any such prima facie case.

Accordingly we reverse the rejection of claims 22, 23, and 34-38 under 35 U.S.C. §103 over Keinanen in view of Sommer '90 and McNamara.

Summary:

We reverse the examiner's rejection of claims 22-23 and 34-38 under 35 U.S.C. § 103 as being unpatentable over Keinanen in view of Sommer '90 and McNamara.

REVERSED

THE NMDA CLASS OF GLUTAMATE RECEPTORS

[77] However, we note the examiner's statement (Answer, page 17) "[t]he Rule 1.131 declaration submitted by [a]ppellants would only be sufficient to effectively establish reduction to practice prior to McNamara for the teaching that there is conservation between the human GluR1-3 compared to rat GluR1-5 as well as human EAA1a and EAA2a receptors, but no additional teaching."

Appeal No. 1996-3140
Application No. 08/164,487

Claims 1, 8, 9 and 15 are illustrative of the subject matter on appeal and are reproduced below:

1. An isolated polynucleotide comprising a nucleotide sequence that codes for a human NMDAR1, wherein said NMDAR1 has the sequence of amino acids 1-867 of SEQ ID NO:2 with none to as many as 6 amino acid substitutions.

8. A process for obtaining a human EAA receptor in substantially homogeneous form, which comprises the steps of culturing cells having incorporated expressibly therein a polynucleotide as defined in claim 1, and then recovering the cultured cells.

9. A process according to claim 8, comprising the subsequent step of obtaining a membrane preparation from the cultured cells.

15. An oligonucleotide comprising at least 17 nucleic acids which hybridizes under stringent conditions with a polynucleotide defined in claim 1.

GROUNDS OF REJECTION[78]

Claim 15 is rejected under 35 U.S.C. § 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the examiner recommends changing the phrase “nucleic acids” to -- nucleotide bases --.

Claim 15 is rejected under 35 U.S.C. § 102(b) as being anticipated by the cDNA that was described in Figure 2 on page 33 of Moriyoshi.

[78] Rejections not referred to in Answer are assumed to have been withdrawn. Ex parte EMM, 118 USPQ 180, 181 (Bd. Pat. App. & Int. 1958). Accordingly, we note the examiner withdrew the provisional rejection of claims 1-11 and 15 under 35 U.S.C. § 101, the rejection of claim 11 under 35 U.S.C. § 112, first paragraph, and the rejection of claim 3 under 35 U.S.C. § 112, second paragraph.

Claims 1-11, 14 and 15 are rejected under 35 U.S.C. § 103 as being unpatentable over Moriyoshi in view of Puckett, Grandy and Zhou.

We affirm the rejection under 35 U.S.C. § 112, second paragraph. We reverse the rejection under 35 U.S.C. § 103. We do not reach the merits of the rejection under 35 U.S.C. § 102(b), and we remand the application to the examiner for further consideration of the 102(b) rejection.

The rejection of claim 15 under 35 U.S.C. § 112, second paragraph:

As set forth in In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989):

> [D]uring patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed. . . . An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process.

The examiner refers (Answer[79], page 4) to page 7, lines 22-25 of Paper No. 9 (mailed September 23, 1994 as the examiner's First Action on the Merits) for the basis of this rejection. At the cited page and lines of Paper No 9, the examiner, referring to claim 15, states "[a]n oligonucleotide is a (emphasis on the singular) nucleic acid and can not "comprise" a plurality of nucleic acids."

We note appellants' original response to this rejection (Paper No. 11, received March 23, 1995), at page 9 appellants state "[t]he amendment to claim 15 should resolve the rejection for lack of clarity in the recitation of an oligonucleotide comprising 'at least about 17 nucleic acids.' Claim 15 now recites 'at least 17

nucleotides ….'" However, contrary to appellants' assertion claim 15 was not amended in Paper No. 11. Claim 15 was later amended in Paper No. 19 (received December 22, 1995) to introduce hybridization conditions, but the amendment addressing the "nucleic acids" was never made.

This failure to amend appears to be an inadvertent error on appellants' part as appellants argue (Brief[80], page 8) that "Moriyoshi does not teach an oligonucleotide comprising '<u>at least 17 nucleotides</u>'" [emphasis added]. However, we must decide the rejection on the basis of the claims as they now appear.

Accordingly we affirm the examiner's rejection of claim 15, under 35 U.S.C. § 112, second paragraph.

<u>The rejection of claim 15 under 35 U.S.C. § 102(b):</u>

The examiner states (Answer, page 4) that "[t]his claim, as amended, encompasses any oligonucleotide which hybridizes under stringent conditions to any polynucleotide which encodes amino acids 1 to 867 of SEQ ID NO:2." The examiner then explains that since the claimed NMDAR1 is at least 99% identical to "the cDNA descried in Figure 2 on page 33 of Moriyoshi." The examiner reasons that given the identity of the sequences the Moriyoshi sequence anticipates the claimed invention.

Appellants argue (Brief, page 8) "that Moriyoshi does not teach an oligonucleotide comprising 'at least 17 nucleotides' which hybridizes under

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[79] Paper No. 21, mailed June 3, 1996.
[80] Paper No.18, received February 22, 1996.

'stringent conditions' with a polynucleotide defined in claim 1, as claimed in claim 15."

We note that the limitation "under stringent conditions" was entered in an amendment (Paper No. 19, received December 22, 1995) filed with appellants' Brief. The examiner entered this amendment. However, upon review of the specification we find reference to hybridization at only three portions of the specification. Specifically, page 9, line 1 "then hybridized, under carefully controlled conditions," page 13, line 39 "by standard hybridization techniques," and page 14, lines 32-35 "hybridization conditions: 6X SSC, 50% formamide, 0.5% SDA, 100 ug/ml denatured salmon sperm DNA at 42ºC …. The filters were washed with 2X SSC, 0.5% SDS at 25ºC for 5 min., followed by 15 min. washes at 37ºC and at 42ºC."

We find no reference to "stringent conditions." Furthermore, appellants' intent appears to be (Brief, page 8) "[t]he subject matter of claim 15, oligonucleotides that hybridize under stringent conditions to a polynucleotide of claim 1, does not include any oligonucleotide the same as those of the rat receptor taught by Moriyoshi." Appellants have not demonstrated that the phrase "stringent conditions" or those conditions recited at page 14 of the specification are capable of satisfying their intention.

We remind the examiner and appellants that analyzing claims based on "speculation as to meaning of the terms employed and assumptions as to the scope of such claims" is legal error. In re Steele, 305 F.2d 859, 862, 134 USPQ 292, 295 (CCPA 1962).

Accordingly, we remand the case to the examiner to first decide whether the amendment to claim 15 was properly entered, and to determine the scope of the claim. Thereafter, the examiner should determine the availability of Moriyoshi as prior art against the claim.

The rejection of claims 1-11, 14 and 15 under 35 U.S.C. § 103:

The examiner states (Answer, page 6) that an "artisan would have found the isolation of a cDNA encoding the human homologue of the rat NMDA receptor of Moriyoshi et.[]al. by employing the expression cloning method described therein but employing a cDNA library prepared from human forebrain mRNA in place of rat mRNA to have been prima facie obvious at the time of the instant invention."

The examiner further states (Answer, page 8) that:

> Because of the known similarities between rat NMDAR1 and rat GluR1 which were disclosed in the Moriyoshi et.[]al. publication and the known similarities between GluR1 and its human homologue as described in Figure 1 on page 7559 of the Puckett et.[]al. publication, an artisan would have reasonably expected a cDNA library which had been prepated [sic] from human brain mRNA to contain a cDNA encoding an NMDAR1 which is analogous both structurally and functionally to the rat NMDAR1 of Moriyoshi et al.

In response appellants argue (Brief, page 17) that "one of ordinary skill might have postulated the existence of a similar human receptor. Until a human homolog actually were isolated, however, its existence and degree of similarity, both structural and functional, to the rat receptor could only have been surmised, not reasonably expected." Appellants then point to a number of differences (Brief, page 25) between the human receptor and the rat receptor.

The examiner responds, inter alia, by stating (Answer, page 11) "[t]here are literally hundreds of prior art publications which describe isolated cDNAs encoding

human receptors in which those receptors were structurally and functionally analogous to rat receptors which were also described therein." While we do not disagree with the examiner's statement, we do disagree with the conclusion he draws from it, based on the facts in this record.

The examiner sets forth Moriyoshi as teaching the rat NMDAR1, Puckett for the teaching that human GluH1 was isolated using a probe from rat GluR1, and two references (Grady and Zhou) which teach cloning cDNA for the human dopamine receptors. However, on this record the examiner does not address which of appellants' receptor variants are reasonably expected to be identified using the methodology set forth in the rejection. Appellants report (specification, page 4, lines 27-30) that "[n]aturally occurring variants include, but are not restricted to, the receptor variants of the human NMDAR1-1 receptor herein designated human NMDAR1-2, NMDAR1-3A, NMDAR1-3B, NMDAR1-3C, NMDAR1-4, NMDAR1-5, NMDAR1-6, NMDAR1-7 and NMDAR1-8."

At the time this invention was made, and on this record, an artisan only had knowledge of Moriyoshi's rat NMDAR1 sequence. There was no recognition, as appellants' note (Brief, page 17), that a human counterpart to the rat receptor existed, let alone that a number of naturally occurring variants existed. In re O'Farrell, 858 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)(obviousness also requires a "reasonable expectation of success").

The examiner's rejection of all the claims requires the successful isolation of a cDNA what encodes the human NMDAR1 receptor(s). In our opinion, on this record, there was no reasonable expectation of successfully isolating such a receptor.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly, we reverse the examiner's rejection of claims 1-11, 15 and 16 under 35 U.S.C. § 103.

Other matters:

The examiner and appellants should reconsider the scope of claim 7 to determine whether the receptor is required to be present on the membrane.[81]

Summary:

We affirm the examiner's rejection of claim 15 under 35 U.S.C. § 112, second paragraph.

We remand the application to the examiner to further develop the rejection of claim 15 under 35 U.S.C. § 102(b) as being anticipated by the cDNA that was described in Figure 2 on page 33 of Moriyoshi.

We reverse the examiner's rejection of claims 1-11, 14 and 15 under 35 U.S.C. § 103 as being unpatentable over Moriyoshi in view of Puckett, Grandy and Zhou.

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 and REMANDED

[81] Compare Appeal No. 2000-1780.

Appeal No. 1999-1377
Application No. 08/264,578

Claim 14 is illustrative of the subject matter on appeal and is reproduced below:

> 14. A method of assaying a candidate ligand for interaction with a human NR3 protein selected from the group consisting of:
>
> NR3-1 having the amino acid sequence of SEQ ID NO:2; and
>
> NR3-2 having the amino acid sequence of SEQ ID NO:2 with the exception that the serine residue at position 407 is an asparagine residue,
>
> which comprises the steps of incubating the candidate ligand under appropriate conditions with a cell having incorporated expressibly therein a heterologous polynucleotide encoding said NR3 protein, or with a membrane preparation derived therefrom, and then determining the extent of binding between the human NR3 protein and the candidate ligand.

GROUNDS OF REJECTION[82]

Claim 21 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellants regard as the invention. Particularly, sections b), c) and d) of this claim reference a modified amino acid sequence, wherein amino acids are replaced by amino acids encoded by the nucleotides of a second sequence.

Claims 14 and 15 are rejected under 35 U.S.C. § 103 as being unpatentable over Monyer in view of Puckett, Schofield and Grenningloh.

[82] We note the examiner made a new ground of rejection over claim 21 in the Examiner's Answer.

Claim 21 is rejected under 35 U.S.C. § 103 as being unpatentable over Monyer in view of Puckett, Schofield and Grenningloh as applied to claims 14 and 15 above, and further in view of Sugihara.

We reverse.

Rejection under 35 U.S.C. § 112, second paragraph:

The examiner states (Answer[83], page 5) that "[s]ince no encoded amino acid sequence is depicted in any of the referenced sequences, which can be read in any one of three frames, and the length of these sequences are not divisible by three then there is no antecedent basis for 'the' amino acid sequence encoded by any on of these sequences."

As stated in In re Morris, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997):

> [T]he PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification.

Appellants argue (Brief, page 10) that:

> The nucleotide sequences of SEQ ID numbers 13, 14 and 15 are substitutions for the nucleotide sequence of SEQ ID NO:10. The deduced amino acid sequence that corresponds to the nucleotide sequence of SEQ ID NO:10 is SEQ ID NO:11. As shown in Figure 7, the nucleotide sequences of SEQ ID numbers 13, 14 and 15 are substituted for a specified nucleotide sequence of SEQ ID NO:10."

[83] Paper No. 20, mailed April 15, 1997.

In our opinion, upon consideration of Figure 7 (Specification), claim 21 read in the light of the specification reasonably apprises those skilled in the art both of the utilization and scope of the invention. We do not find the claim indefinite.

Accordingly, we reverse the rejection of claim 21 under 35 U.S.C. § 112, second paragraph[84].

Rejections under 35 U.S.C. § 103:

The rejection of claims 14 and 15:

The examiner states (Answer, page 9) that:

> [T]he combination of the Puckett et al., Schofield et al. and Grenningloh et al. publications provided a reasonable expectation that the sequence and structure of the NR1 and NR2B subunits of Monyer et al. were predictive of a human homologous proteins, they would have found it prima facie obvious to have isolated cDNAs encoding human NR1 (NMDAR1) and NR2B (NR3) by screening a human cDNA library like the one described … [by] Puckett … Schofield … and … Grenningloh … with a nucleic acid probe corresponding to the rat NR1 and NR2B cDNAs of Monyer et al. in a manner that was directly analogous to those that were employed by each of Puckett et al., Schofield et al. and Grenningloh et al.

Claim 14:

Appellants argue (Brief, page 14) that:

> Given knowledge a rat or any other, non-human receptor subunit protein, the skilled artisan may postulate as to the existence of a similar human receptor subunit protein, but until that receptor is actually isolated, its existence and degree of similarity to the rat receptor subunit protein with respect to sequence and function, can only be surmised, not reasonably expected.

The examiner identifies (Answer, page 6) figure 1 (page 1218) of Monyer as teaching four putative transmembrane domains that are believed to be common to all ionotrophic receptor subunits. We note that this figure recites the sequences of

[84] In reversing the examiner's rejection under 35 U.S.C. § 112, second paragraph, we note 37 CFR § 1.822(o) discussed infra, with regard to Appeal No. 2000-0440.

NR2A, NR2B and NR2C. Monyer teaches (page 1217, bridging paragraph, columns 1-2) that "[b]y polymerase chain reaction (PCR) amplification of rat brain cDNA with oligonucleotides constructed to detect such conserved sequences … we found three cDNAs encoding new glutamate receptor subunits, termed NMDAR2A (NR2A), NR2B, and NR2C (Fig. 1)."

The examiner notes (Answer, page 6) the human "NR3 of the instant invention as depicted in SEQ ID NO:2 of the instant application is 97% identical to the amino acid sequence of the NR2B protein that was depicted in Figure 1 of the Monyer et al. publication and, therefore, NR3 is clearly the human homolog of NR2B."

Claim 15:

Appellants argue (Brief, page 27) that:

> The examiner has not explained why the combination of references would have suggested a method of assaying for a heteromeric complex of human NR3 protein and human NMDA protein. Just as the art does not suggest a human counterpart to Monyer's NR2B receptor subunit, the art also does not suggest a human NMDA protein, as recited in claim 15.

Lacking from the examiner's rejection is any reference to the claimed proteins, specifically NR3-1 and NR3-2. The examiner merely refers to NR3 generically. See e.g., Answer, page 6 ("therefore, NR3 is clearly the human homolog of NR2B"). It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

On this record, we see no suggestion that would lead one of ordinary skill in the art to obtain NR3-1 or NR3-2 having the sequences recited in the claims. In re Ochiai, 71 F.3d 1565, 1570, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). We also do not find that there was a reasonable expectation that one could have obtained such a receptor sequence required to perform the claimed methods, based on the existence of the three receptor types NR2A-C taught by Monyer. In re O'Farrell, 858 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)(obviousness also requires a "reasonable expectation of success").

Even had there been a reasonable expectation of success we find no suggestion, absent the information found in appellants' specification, to use NR2B instead of NR2A or NR2C to obtain the claimed NR3-1 and NR3-2 receptors. Each of Puckett, Schofield and Grenningloh fail to make up this deficiency.

Based on the combination of references applied by the examiner, without first obtaining a cDNA for NR3-1 or NR3-2 the claimed method could not be obtained. On this record, we find that the examiner failed to meet his burden of establishing a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

Having found that the examiner failed to meet his burden of establishing a prima facie case of obviousness in obtaining the NR3-1 and NR3-2 protein, the claimed assay method of claim 14 would not have been obvious. In addition, since the examiner failed to meet his burden of establishing a prima facie case of obviousness in obtaining the NR3-1 and NR3-2 protein, we need not discuss the

NMDA protein used in a heteromeric receptor complex with NR3 protein of claim 15.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly we reverse the rejection of claims 14 and 15 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of Puckett, Schofield and Grenningloh.

The rejection of claim 21:

The examiner relies (Answer, page 10) upon Sugihara for the teaching of rat homologs of the recited NMDAR1 variants. However, Sugihara does not make up for the deficiencies in the combination of Monyer in view of Puckett, Schofield and Grenningloh, supra.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly, we reverse the rejection of claim 21 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of Puckett, Schofield and Grenningloh as applied to claims 14 and 15 above, and further in view of Sugihara.

Summary:

We reverse the examiner's rejection of claim 21 under 35 U.S.C. § 112, second paragraph.

We reverse the examiner's rejection of claims 14 and 15 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of Puckett, Schofield and Grenningloh.

We reverse the examiner's rejection of claim 21 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of Puckett, Schofield and Grenningloh as applied to claims 14 and 15 above, and further in view of Sugihara.

REVERSED

Appeal No. 2000-0440
Application No. 08/217,704

Claim 14 is illustrative of the subject matter on appeal and is reproduced below:

14. A method of assaying a candidate ligand for binding interaction with a human NR2A protein, which comprises the steps of:
    (1) incubating the candidate ligand under appropriate conditions with a cell that has been mutated to produce a human NR2A protein,
        said cell having incorporated expressibly therein a heterologous polynucleotide that encodes a modulatory protein selected from the group consisting of NR2A-1 having the amino acid sequence of SEQ ID NO:2 and NR2A-2 having the amino acid sequence of SEQ ID NO:2 wherein the lysine at position 270 is replaced by glutamic acid,
        or with a membrane preparation containing said NR2A protein, and then
    (2) determining the extent of binding between the human NR2A protein and the candidate ligand.

GROUNDS OF REJECTION

Claims 14, 21 and 22 are rejected under 35 U.S.C. § 103 as being unpatentable over Monyer in view of McNamara, Blackstone, Schofield, Grenningloh and Puckett.

Claims 23 and 34 are rejected under 35 U.S.C. § 103 as being unpatentable over Monyer in view of McNamara, Blackstone, Schofield, Grenningloh and Puckett as applied to claims 14, 22, and 23 above and further in view of Durand.

We reverse.

The rejections under 35 U.S.C. § 103:

The initial burden of establishing reasons for unpatentability rests on the examiner. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Furthermore, to establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

The rejection of claims 14, 21 and 22:

The examiner states (Answer[85], bridging paragraph, pages 9-10) that:

> [T]he combination of the McNamara et al., Blackstone et al., Puckett et al., Schofield et al. and Grenningloh et al. publications provided overwhelming evidence that the genes encoding ionotrophic receptor subunits and the proteins encoded thereby were highly conserved both structurally and functionally between mammalian species and a reasonable expectation that the sequence and structure of the NR1 and NR2B subunits of Monyer et al. were predictive of a human homologous proteins, that artisan would have found it prima facie obvious to have isolated cDNAs encoding human NR1 (NMDAR1) and NR2B (NR3) by screening a human cDNA library like the one described … [by] Puckett … Schofield … and … Grenningloh et al. with a nucleic acid probe corresponding to the rat NR1 and NR2B cDNAs of Monyer et al. in a manner that was directly analogous to those that were employed by each of Puckett et al., Schofield et al. and Grenningloh et al.

The examiner further states (Answer, page 11) that:

> The rejection is based upon the fact that a comparison of the amino acid sequence presented in Figure 1 (SEQ ID NO:2) of the instant application, which is recited in the claims under appeal, with the amino acid sequence presented as NR2A in Figure 1 of Monyer et al. shows that these two sequences from these two naturally occurring mammalian proteins are greater than 95% identical. … The preponderance of evidence of record supports a conclusion that an

[85] Paper No. 32, mailed February 10, 1999.

> isolated DNA encoding any one of these proteins [NR2A, NR2B, NR2C and NR1], as well as the protein encoded thereby, would have reasonably been expected to be predictive of the existence, structure and function of an analogous DNA and protein from any other mammal.

Lacking from the examiner's rejection is any reference to the claimed proteins, specifically NR2A-1 and NR2A-2. The examiner merely refers to NR2A generically, throughout the body of the Answer. It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

On this record, we see no suggestion that would lead one of ordinary skill in the art to obtain NR2A-1 or NR2A-2 having the sequences recited in the claims. In re Ochiai, 71 F.3d 1565, 1570, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). Contrary to the examiner's position, we also do not find that there was a reasonable expectation that one could have obtained such a receptor sequence, having the claimed sequences, required to perform the claimed methods, based on the existence of the three rat receptors NR2A-C taught by Monyer. In re O'Farrell, 858 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)(obviousness also requires a "reasonable expectation of success").

Based on the combination of references applied by the examiner, without first obtaining a cDNA for NR2A-1 or NR2A-2 the claimed method could not be obtained. On this record, we find that the examiner failed to meet his burden of

establishing a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

Having found that the examiner failed to meet his burden of establishing a prima facie case of obviousness in obtaining the NR2A-1 and NR2A-2 protein, the claimed assay method of claim 14 would not have been obvious. In addition, since the examiner failed to meet his burden of establishing a prima facie case of obviousness in obtaining the NR2A-1 and NR2A-2 protein, we need not discuss the NMDAR1 receptor unit used in a heteromeric receptor complex with NR3 protein of claim 21.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly we reverse the rejection of claims 14, 21 and 22 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of McNamara, Blackstone, Schofield, Grenningloh and Puckett.

The rejection of claims 23 and 34:

The examiner relies (Answer, page 10) upon Durand for the teaching that the rat NMDAR1 receptor subunit was known to occur in eight splicing variants. However, Durand does not make up for the deficiencies in the combination of Monyer in view of McNamara, Blackstone, Schofield, Grenningloh and Puckett.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly, we reverse the rejection of claims 23 and 34 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of McNamara, Blackstone, Schofield, Grenningloh and Puckett as applied to claims 14, 22 and 23 above and further in view of Durand.

Other Matters:

We note the examiner's comments (Answer, page 4) that the "instant claims do not comply with 37 CFR § 1.822(o) which states '[a] sequence that is made up of one or more noncontiguous segments of a larger sequence or segments from different sequences shall be presented as a separate sequence." In our opinion, the examiner should address the claims of related Appeal No. 1999-1377, supra, in the same manner as they were treated here.

Summary:

We reverse the examiner's rejection of claims 14, 21 and 22 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of McNamara, Blackstone, Schofield, Grenningloh and Puckett.

We reverse the examiner's rejection of claims 23 and 34 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of McNamara, Blackstone, Schofield, Grenningloh and Puckett as applied to claims 14, 22 and 23 above and further in view of Durand.

REVERSED

CUMMULATIVE SUMMARY

Kainate Receptors:

Appeal No. 1999-0350: Reversed

We reverse the examiner's rejection of claims 23, 25, 26, 37, 39, and 43-45 under 35 U.S.C. § 103(a) as being unpatentable over Heinemann in view of Bettler '90, Sommer '92, Puckett and Birnbaumer.

Appeal No. 1997-3221: Reversed

We reverse the examiner's rejection of claims 26, 27, 40, 45, and 47-52 under 35 U.S.C. § 103 as being unpatentable over Egebjerg in view of either Sun or Puckett.

We reverse the examiner's rejection of claim 28 under 35 U.S.C. § 103 as being unpatentable over Egebjerg, Puckett, and Sun as applied to claim 26, 27, 40, 45, and 47-52 and further in view of Cutting.

Appeal No. 1998-0217: Reversed, 37 CFR § 1.196(b)

We reverse the examiner's rejection of claims 35, 37, and 38 under 35 U.S.C. § 103 as being unpatentable over Bettler in view of Puckett.

We reverse the examiner's rejection of claims 35, 37, and 38 under 35 U.S.C. § 103 as being unpatentable over Werner in view of Heinemann and Puckett.

We make the following New Ground of Rejection under 37 CFR § 1.196(b). Claims 35-38 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Appeal No. 1999-0399: Reversed

We reverse the examiner's rejection of claims 1, 2, 8-21, and 40 under 35 U.S.C. § 103 as being unpatentable over Bettler '92 in view of Puckett.

AMPA Receptors:

Appeal No. 1997-3377: Reversed

We reverse the examiner's rejection of claims 31, 33, 34, and 37-40 under 35 U.S.C. § 103 over Puckett in view of Cutting.

Appeal No. 1999-1393: Reversed

We reverse the examiner's rejection of claims 1-16 under 35 U.S.C. § 103 over Heinemann in view of Puckett and Sun.

Appeal No. 1999-2118: Reversed

We reverse the examiner's rejection of claims 22, 32, and 34-40 under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett and Sun.

We reverse the examiner's rejection of claims 31 and 33 under 35 U.S.C. § 103 as being unpatentable over Heinemann, Puckett, and Sun as applied to claims 22, 32, and 34-40 above and further in view of Cutting.

Appeal No. 1999-2200: Affirmed-in-Part, 37 CFR § 1.196(c)

We affirm the examiner's rejection of claims 23 and 24 under 35 U.S.C. § 102(b) as being anticipated by Cutting.

We reverse the examiner's rejection of claims 1, 4, 7, 10, 11, 13, 15, 16, 18, 19, 26, and 42-49 are rejected under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett, Sun, Schofield, and Grenningloh.

We reverse the examiner's rejection of claims 23, 24 and 27 are rejected under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett, Sun, Schofield, and Grenningloh as applied to claims 1, 4, 7, 10, 11, 13, 15, 16, 18, 19, 26, and 42-49 above, and further in view of Cutting.

Appeal No. 2000-1778: Reversed

We reverse the examiner's rejection of claims 28, 43-45, and 49-52 under 35 U.S.C. § 103 as being unpatentable over Heinemann in view of Puckett and Sun.

Appeal No. 2000-1779: Affirmed-in-Part

We affirm the rejection of claims 17 and 19 under 35 U.S.C. § 103 as being unpatentable over the combination of McNamara and Sommer '90.

We reverse the examiner's rejection of claim 31 under 35 U.S.C. § 103 as being unpatentable over the combination of McNamara and Sommer '90.

Appeal No. 2000-1780: Reversed

We reverse the examiner's rejection of claims 22-23 and 34-38 under 35 U.S.C. § 103 as being unpatentable over Keinanen in view of Sommer '90 and McNamara.

NMDA Receptors:

Appeal No. 1996-3140: Affirmed-in-Part and Remanded

We affirm the examiner's rejection of claim 15 under 35 U.S.C. § 112 second paragraph.

We remand the application to the examiner to further develop the rejection of claim 15 under 35 U.S.C. § 102(b) as being anticipated by the cDNA that was described in Figure 2 on page 33 of Moriyoshi.

We reverse the examiner's rejection of claims 1-11, 14 and 15 under 35 U.S.C. § 103 as being unpatentable over Moriyoshi in view of Puckett, Grandy and Zhou.

Appeal No. 1999-1377: Reversed

We reverse the examiner's rejection of claim 21 under 35 U.S.C. § 112, second paragraph.

We reverse the examiner's rejection of claims 14 and 15 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of Puckett, Schofield, and Grenningloh.

We reverse the examiner's rejection of claim 21 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of Puckett, Schofield, and Grenningloh as applied to claims 14 and 15 above, and further in view of Sugihara.

Appeal No. 2000-0440: Reversed

We reverse the examiner's rejection of claims 14, 21 and 22 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of McNamara, Blackstone, Schofield, Grenningloh, and Puckett.

We reverse the examiner's rejection of claims 23 and 34 under 35 U.S.C. § 103 as being unpatentable over Monyer in view of McNamara, Blackstone, Schofield, Grenningloh, and Puckett as applied to claims 14, 22 and 23 above and further in view of Durand.

	)
William F. Smith	)
Administrative Patent Judge	)
	)
	)
	) BOARD OF PATENT
Donald E. Adams	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
	)
Demetra J. Mills	)
Administrative Patent Judge	)

APPENDIX A

Identification of Inventors, Appeal No., and Application No. of Each Appeal Discussed in this Consolidated Decision

Ex Parte:	Appeal No.:	Application No.:
ROBERT L. FOLDES, and RAJENDER KAMBOJ	1996-3140	08/164,487
RAJENDER KAMBOJ, CANDACE E. ELLIOTT, and STEPHEN L. NUTT	1997-3221	08/249,241
RAJENDER KAMBOJ, CANDACE E. ELLIOTT, and STEPHEN L. NUTT	1997-3377	08/216,326
RAJENDER KAMBOJ, CANDACE E. ELLIOTT, and STEPHEN L. NUTT	1998-0217	08/178,019
RAJENDER KAMBOJ, CANDACE E. ELLIOTT, and STEPHEN L. NUTT	1999-0350	08/189,738
RAJENDER KAMBOJ, CANDACE E. ELLIOTT, and STEPHEN L. NUTT	1999-0399	08/377,503
ROBERT L. FOLDES, SALLY-LIN ADAMS, and RAJENDER KAMBOJ	1999-1377	08/264,578
RAJENDER KAMBOJ, CANDACE E. ELLIOTT, and STEPHEN L. NUTT	1999-1393	08/242,344
RAJENDER KAMBOJ, CANDACE E. ELLIOTT, and STEPHEN L. NUTT	1999-2118	08/439,946
RAJENDER KAMBOJ, CANDACE E. ELLIOTT, and STEPHEN L. NUTT	1999-2200	08/896,063
ROBERT FOLDES, ROBERT FANTASKE, SALLY-LIN ADAMS, and RAJENDER KAMBOJ	2000-0440	08/217,704
RAJENDER KAMBOJ, CANDACE E. ELLIOTT, and STEPHEN L. NUTT	2000-1778	08/257,029
RAJENDER KAMBOJ, CANDACE E. ELLIOTT, and STEPHEN L. NUTT	2000-1779	08/473,204
RAJENDER KAMBOJ, CANDACE E. ELLIOTT, and STEPHEN L. NUTT	2000-1780	08/403,663

APPENDIX B

This Table Illustrates the Appeals and United States Patents Relating to this Receptor Family

KAINATE:					AMPA:				NMDA:
EAA1	EAA2	EAA3C &EAA3D	EAA4	EAA5	GLUR1	GLUR2	GLUR3	GLUR4	R1
		1999-0350	1997-3221	1998-0217	1997-3377	1999-1393	1999-2200	2000-1779	1996-3140
				1999-0399		1999-2118	2000-1778	2000-1780	1999-1377
									2000-0440
5,576,205	5,494,792	5,547,855	5,574,144		5,610,032	6,040,175		5,643,785	
5,616,481	5,614,406	6,018,023							
6,013,768	5,981,704								

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