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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte PER-OLOF BERGGREN, ALEJANDRO CAICEDA, and OVER CABRERA.[1]

Appeal 2015-006838
Application 13/847,212
Technology Center 1600

Before RICHARD M. LEBOVITZ, JEFFERY N. FREDMAN, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

SCHNEIDER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method for treating hypoglycemia which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

The claimed invention is directed to methods for treating hypoglycemia. Spec. ¶ 9. The method comprises administering an effective

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[1] Appellants identify the Real Party in Interest as Biocrine, AB. Appeal Br. 3.

amount of a compound that activates an ionotropic glutamate receptor to stimulate glucagon release. Spec. ¶ 10.

Claims 1–7 are on appeal. Claim 1 is illustrative and reads as follows:

> 1. A method of treating hypoglycemia comprising administering to a primate an effective amount of a compound that activates an ionotropic glutamate receptor to stimulate glucagon release.

The claims stand rejected as follows:

Claims 1–5 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Bertrand[2] in view of Sarkar[3], Huth[4] and Samaan[5].

Claim 6 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Bertrand, Huth and Samaan in view of Ligon[6].

Claim 7 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Bertrand, Huth, Samann and Ligon in view of Hodgson[7].

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[2] Bertrand et al, *Glutamate stimulates glucagon secretion via excitatory amino acid receptor of AMPA subtype in rat pancreas,* 237 EUR. J.. PHARM. 45–50 (1993) ("Bertrand").

[3] Sarkar et al., *Demonstration of Hypoglycemic Action of Momordica Charantia in a Validated Animal Model of Diabetes,* 33 PHARM. RES. 1, 1–4 (1996) ('Sarkar").

[4] Huth et al., US 6,288,065 B1, issued Sept, 2001("Huth").

[5] Samann et al., *Successful Treatment of Hypoglycemia Using Glucagon in a Patient with an Extrapancreatic Tumor,* 113 ANN. INTERN. MED. 404–405 (1990) ("Samaan").

[6] Ligon, US 2003/0162754 A1, published Aug. 28, 2003 ("Ligon").

[7] Hodgson et al., US 2004/0014087 A1, published Jan. 22, 2004 ("Hodgson").

DISCUSSION

Issue

In rejecting claims 1–5, the Examiner finds that Bertrand teaches the administration of compounds such as quisqualate, kainite and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) to stimulate glucagon release. Final Act. 3. The Examiner finds that while Bertrand does not teach the administration of the compounds to primates, one skilled in the art would have a reasonable expectation of success of using the compound for primates as rat models are commonly used for investigation primate related diseases associated with hypoglycemia given the teachings of Sarkar. *Id.* The Examiner also finds that Huth teaches that compounds that are highly specific to AMPA receptors can be used to treat diseases such as hypoglycemia. Final Act. 4. With respect to Samaan, the Examiner finds that Samaan teaches that glucagon can be used to treat hypoglycemia. Final Act. 5.

The Examiner concludes that

> [o]ne of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed based on the combined teachings of Bertrand, Huth, and Samaan. One of ordinary skill in the art would have recognized from the teaching of Bertrand that compounds such as quisqualate, kainate and AMPA are effective in stimulating glucagon release and that generally, compounds which are highly specific for AMPA receptors are useful in treating hypoglycemia as taught in Huth. One of ordinary skill in the art would have also recognized from teaching of Samaan that glucagon is associated with the effective treatment of hypoglycemia. Therefore, it would have been obvious to one of ordinary skill in the art to generate a method of treating hypoglycemia by administering compounds such as AMPA,

> kainate, or quisqualate to stimulate glucagon release. Therefore, the invention as a whole was prima facie obvious at the time it was invented.

Final Act. 5.

Appellants contend that the references do not teach or suggest the present invention. Appeal Br. 6. Appellants point out that the Examiner conceded that Bertrand does not teach administration of the claimed compounds to primates. *Id.* With respect to Sarkar, Appellants argue that Sarkar related to the treatment of diabetes which is the opposite of hypoglycemia. Appeal Br. 6–7. Appellants argue that one skilled in the art would not read Sarkar as teaching that a rat model could be used to study hypoglycemia in primates. Appeal Br. 7. Appellants next argue that Huth does not correct the deficiencies of Bertrand and Sarkar as Huth actually teaches away from using the recited compounds to treat hypoglycemia in that it teaches that the compounds are AMPA antagonists, not activators. Appeal Br.. 7–8. Appellants also argue that neither Ligon nor Hodgson address the deficiencies of the other references. Appeal Br. 8.

Appellants further argue that one skilled in the art would not have a reasonable expectation of success in using the claimed compounds to treat hypoglycemia as the art at the time of the invention was contradictory and unpredictable. Appeal Br. 9. Appellants argue that the Uehara[8] article

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[8] Uehara et al., *Metabotropic Glutamate Receptor Type 4 is Involved in Autoinhibitory Cascade for Glucagon Secretion by α-Cells of Islet of Langerhans,* 53 DIABETES 998–1006 (2004) ("Uehara").

teaches that the claimed compounds actually act as inhibitors of glucagon release, the exact opposite of Bertrand. Appeal Br 9–11.

The issue with respect to this rejection is whether the Examiner has established by a preponderance of the evidence that claims 1–7 would have been obvious over the cited references as defined by 35 U.S.C. § 103(a).

Findings of Fact

We adopt as our own the Examiner's findings and analysis. The following findings are included for emphasis and reference convenience.

FF1. Bertrand teaches that "L-glutamate stimulates glucagon release in rat pancreas by activating a receptor of the AMPA subtype." Bertrand Abstract. The AMPA receptor is a glutamate receptor. Bertrand 45.

FF2. Bertrand also teaches that AMPA, quisqualate and kainite also stimulate glucagon release. Bertrand 47.

FF3. Sarkar teaches that a rat model can be used to validate the hypoglycemic activity of a fruit extract in human diabetes mellitus. Sarkar 4.

FF4. Samaan teaches that glucagon administration successfully controlled hypoglycemia. Samaan 405.

FF5. Uehara discloses that L-glutamate inhibits glucagon secretion from isolated islets under low-glucose conditions and that AMPA and Kainate did not stimulate glucagon secretion under low-glucose conditions. Uehara 1002 ("Discussion").

FF6. Table 1, reproduced below, lists the effects of L-glutamate and agonists of GluRs (glutamate receptor) on low-glucose-dependent glucagon secretion. Uehara 1002

TABLE 1
The effects of L-glutamate and agonists of GluRs on low-glucose- dependent glucagon secretion

Additions	Concentration (μmol/l)	Glucagon release (ng ·20 islets-¹· 30 min-¹
16.7 16.7 (basal release)	1,000	0.51 :±:: 0.23*
16.73.3 (100% control)	1,000	1.67 ± 0.17
+ L-glutamate	1,000	0.66 :±:: 0.19*
+ L-glutamate + 100 μmol/l CPPG	1,000	2.43 :±:: 0.16*
+ L-glutamate + 300 nmoLl1 LY311195	1,000	0.69 :±:: 0.12*
+ L-glutamate + 30 μmol/l LY341495	1,000	1.62 :±:: 0.15 NS
+ PPG	0.04	1.65 :±:: 0.13 NS
+ PPG	0.1	1.49 :±:: 0.18 NS
+ PPG	1	1.34 :±:: 0.16t
+ PPG	10	1.10 :±:: 0.20:j:
+ PPG	100	0.73 :±:: 0.10*
+ PPG + 100 μmol/l CPPG	100	2.38 :±:: 0.20:j:
+ DCPG	0.02	1.72 :±:: 0.13 NS
+ DCPG	0.1	1.60 :±:: 0.18 NS
+ DCPG	1	1.48 :±:: 0.15 NS
+ DCPG	10	1.32 :±:: 0.18t
+ DCPG	100	0.82 :±:: 0.12*
+ DCPG + 100 μmol/l CPPG	100	2.25 :±:: 0.21:j:
+ ACPT-I	1	1.61 :±:: 0.13 NS
+ ACPT-I	10	1.09 :±:: 0.23:j:
+ ACPT-I	20	0.92 :±:: 0.17*
+ ACPT-I	50	0.66 :±:: 0.11*
+ ACPT-I	100	0.68 :±:: 0.20*
+ ACPT-I + 100 μmol/l CPPG	50	2.37 :±:: 0.14*
+ CPPG	100	2.28 :±:: 0.19:j:
+ (S)3,5DHPG	1,000	1.73 :±:: 0.18 NS
+ Quisqualate	1,000	1.36 :±:: 0.15t
+ L-CCG-I	100	1.57 :±:: 0.19 NS
+ *trans-ACPD*	1,000	1.54 :±:: 0.13 NS
+ AMPA	500	1.37 :±:: 0.21§
+ Kainate	500	1.33 :±:: 0.15t

Data are means :±:: SE, $n = 4$. Isolated islets (20 pieces per assay) were first incubated with a solution containing 16.7mmol/l glucose, and then transferred to a solution containing 3.3 mmol/l glucose to induce glucagon secretion in the presence or absence of the listed compounds at the indicated concentrations. After incubation for 30 min, the medium was carefully sampled and the

amount of glucagon was determined. Glucagon secretion with 16.7 mmol/l glucose throughout is also shown as basal release. $*P < 0.001$; tP < 0.05; $tP < 0.01$; $\S P < 0.1$. NS, not significant vs. 100% control.

Principles of Law

"The factual predicates underlying an obviousness determination include the scope and content of the prior art, the differences between the prior art and the claimed invention, and the level of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1355, (Fed. Cir. 1998).

"In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted).

"Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986).

The "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success. . . . Indeed, a rule of law equating unpredictability to patentability . . . would mean that any new salt—including those specifically listed in the [prior art patent] itself—would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard

since the expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

Analysis

Because the same issues are dispositive for all of these rejections, and all of the rejections rely upon Bertrand, Samaan and Huth, we will consider them together.

Claim 1 is representative of the rejected claims and is directed to a method of treating hypoglycemia by administering a compound that activates a glutamate receptor to stimulate glucagon secretion.

We agree with the Examiner that the subject matter of claim 1 would have been obvious at the time the invention was made. Bertrand teaches that compounds such as glutamate, kainate and quisqualate stimulate glucagon secretion in rats. FF1 and 2. These compounds activate glutamate receptors.. Although Bertrand does not explicitly teach that glucagon secretion can be used to treat hyperglycemia, Samaan teaches that glucagon can be used to treat hypoglycemia. FF3. Sarkar teaches that rats can be used to model human diseases involving glucose levels, providing evidence Bertrand's results in rats would be viewed as applicable to primates. Thus, the Examiner's finding that "it would have been obvious to one of ordinary skill in the art to generate a method of treating hypoglycemia by administering compounds such as AMPA, kainate, or quisqualate to stimulate glucagon release" is supported by the evidence. Final Act. 5.

Appellants contend that the references do not teach the elements of claim 1. Appellants point to the fact that Bertrand does not relate to the treatment of primates and that Sarkar is not directed to hypoglycemia but

rather diabetes. Appeal Br. 6–7. Appellants also argue that Huth teaches away from the present invention, and that Samaan does not disclose activating an ionotropic glutamate receptor. Appeal Br. 7–8. We are unpersuaded. The rejection is based on the teachings of the references together and not individually. While Bertrand only discussed simulation in rats, as the Examiner points out, Sarkar shows the applicability of a rat model to development of a treatment of humans. Ans. 6–7. Samaan and Huth provide the nexus between administration of glutamate and treatment of hypoglycemia. Ans. 6. Thus, the reference read together render the subject matter of claim 1 obvious.

Appellants contend that "Huth teaches that compounds that antagonize (i.e., inhibit) AMPA receptors are suitable for treating a number of diseases, among them hypoglycemia." Appeal Br. 8. However, Appellants contend that their claims involve activation and stimulation of glutamate receptors. *Id*. Thus, Appellants contend that the Huth teaches away from the claimed invention.

This argument does not persuade us that the Examiner erred. While Huth contains statements the specific quinoxaline compounds are antagonists that can be used to treat hypoglycemia (e.g., Huth, col. 3, l. 60 to col. 4, ll. 1–10, we note that the term "hypoglycemia" appears in a longer list of diseases which appears to be speculative. On the other hand, Bertrand provide experimental evidence of specific compounds that activate a glutamate receptor (AMPA) and cause glutamate release which has a nexus to treatment of hypoglycemia. First, we consider the experimental evidence of Bertrand to be more compelling than the statements in Huth. Second, the

compounds in Huth are different from those in Bertrand, and thus not necessarily inconsistent with Bertrand.

Appellants next argue that one skilled in the art would not have had a reasonable expectation of success in using the claimed compounds to treat hypoglycemia. Appeal Br. 9. Appellants point to the teachings of Uehara to demonstrate that the teachings in the art were contradictory and unpredictable. Appeal Br. 9–12. We remain unpersuaded. Claim 1 is not limited to the use of glutamate but embraces other compounds including AMPA, kainate and quisqualate. Bertrand teaches that all four compounds stimulate glucagon secretion. F1 and F2. Uehara only states that glutamate is a glucagon inhibitor at low glucose concentrations. FF5. With respect to AMPA and kainate, while Uehara states that these compounds do not stimulate glucagon release, FF5, Table 1 of Uehara shows that these compounds stimulate glucagon release at levels above the basal level. FF6. Quisqualate exhibits similar levels of glucagon release. *Id.* Uehara also teaches:

> AMPA and kainate, but not N-methyl-D-aspartate, were also shown to stimulate glucagon secretion from perfused pancreas (15). However, under low-glucose conditions, L-glutamate secreted from [alpha]-cells stimulates an AMPA-type receptor and selectively triggers [gamma]-aminobutyric acid (GABA) secretion, with a lower effect on insulin secretion in isolated islets and clonal [beta]clonal [3-cells (4).

Uehara 908. Thus, Uehara doesn't say that AMPA and kainite would not work under low-glucose conditions, just that the effect would be lowered.

We have considered the declaration of Dr. Berggren[9] and find it unpersuasive. Dr. Berggren does not address the teachings of Uehara discussed above that show that AMPA and kainante do stimulate glucagon production, but at lower levels. Berggren Decl. ¶¶ 10 & 11. With respect to Dr. Berggren's discussion of rat models versus primates, Dr. Berggren does not address the teaching of Sarkar which shows the applicability of rat models, FF3, nor does Dr. Berggren point to any teaching in the art which would lead one skilled in the art to conclude that rat models are not applicable to primates. Berggren Decl. ¶ 13.

In addition to this, in view of Bertrand's report that certain glutamate receptor agonists stimulate glucagon release, the skilled worker would have had reason to try such agonists to treat hypoglycemia as discussed above. Even if Uehara results are not identical to those of Bertrand, there are only a finite number of solutions described in the cited publications. "[W]here a skilled artisan merely pursues 'known options' from a 'finite number of identified, predictable solutions,' obviousness under § 103 arises. [*KSR Int'l Co. v. Teleflex Inc.*,] 550 U.S. at 421, 127 S.Ct. 1727." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). Appellants have not identified anything different they did to make the known glutamate receptor agonists work; rather, they administered them to stimulate glucagon release exactly in the manner described in the prior art.

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[9] Declaration of Per-Olof Berggren Under 37 C.F.R. 1.132 filed Mar 19, 2013 ("Berggren Decl.").

Thus, one skilled in the art would conclude from the teachings of Bertrand and Uehara that AMPA, kainate and quisqualate stimulate glucagon release and would have a reasonable expectation that the compounds could be used to treat hypoglycemia.

With respect to claims 6 and 7, Appellants' only argument is that neither Ligon nor Hodgson cure the deficiencies of the other references. Appeal Br. 8. As discussed above, there is no deficiency in the teachings of Bertrand combined with Sarkar, Huth and Samaan.

Conclusion of Law

We conclude that the Examiner has established by a preponderance of the evidence that claims 1, 6 and 7 would have been obvious over Bertrand combined with Sarkar, Huth and Samaan under 35 U.S.C. § 103(a).

Claims 2–5 have not been argued separately and therefore, fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

We affirm the rejections under 35 U.S.C. § 103(a).

TIME PERIOD FOR RESPONSE

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

AFFIRMED