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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* RENE ETCHEBERRIGARAY and DANIEL L. ALKON

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Appeal 2011-003547  
Application 10/933,536  
Technology Center 1600

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Before JEFFREY N. FREDMAN, STEPHEN WALSH, and  
ULRIKE W. JENKS, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims directed to methods of enhancing cognitive ability, reducing amyloid plaque, treating Alzheimer's Disease, and achieving other goals, by administering a macrocyclic lactone. The Examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

## STATEMENT OF THE CASE

The Specification is directed to:

[M]ethods for the treatment of conditions associated with enhancement/improvement of cognitive ability. . . .  
[specifically] for the treatment of conditions associated with amyloid processing, such as Alzheimer's Disease, which provides for improved/enhanced cognitive ability in the subject treated. In particular the compounds and compositions of the present invention are selected from macrocyclic lactones (i.e. bryostatin class and neristatin class).

(Spec. 6, ll. 6-11.)

Claims 1, 2, 4-13, 19-25, 27, 28, 30, 34, 36, and 37 are on appeal, and can be found in the Claims Appendix of the Appeal Brief (App. Br. 33-37). Claims 1, 19, 23, 28, 30, 34, 36, and 37 are independent claims. Claim 1 is representative of the claims on appeal, and reads as follows:

1. A method for enhancing cognitive ability in a human or animal subject in need thereof, comprising administering to said human or animal subject a macrocyclic [sic] lactone in a pharmaceutically acceptable carrier in an amount effective for enhancing cognitive ability.

Appellants do not request review of the following rejections:

- i. claims 1, 2, 4-13, 19-25, 27, 28, 30, and 34-37 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,825,229 (Ans. 4; Final Office Action 2);

- ii. claims 1, 2, 4-13, 19-25, 27, 28, 30, and 34-37 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12-61 of co-pending Application No. 10/937,509 (Ans. 5; Final Office Action 2); and
- iii. claims 1, 2, 4-13, 19-25, 27, 28, 30, and 34-37 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 104-133 of co-pending Application No. 11/802,842 (Ans. 5; Final Office Action 3).

We therefore summarily affirm them. *See* MANUAL OF PATENT EXAMINING PROCEDURE § 1205.02 (“If a ground of rejection stated by the examiner is not addressed in the appellant’s brief, that ground of rejection will be summarily sustained by the Board.”). *Ex parte Frye*, 2010 WL 889747 \*4 (BPAI 2010) (precedential) (“If an appellant fails to present arguments on a particular issue—or, more broadly, on a particular rejection—the Board will not, as a general matter, unilaterally review those uncontested aspects of the rejection”).

The following ground of rejection is before us for review:

The Examiner has rejected claims 1, 2, 4-13, 19-25, 27, 28, 30, 34, 36, and 37 under 35 U.S.C. § 103(a) as unpatentable over Chui<sup>1</sup> or Tamura,<sup>2</sup> in view of Pettit,<sup>3</sup> McGown,<sup>4</sup> Ibarreta,<sup>5</sup> and Driedger.<sup>6</sup>

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<sup>1</sup> Chui et al., JP 2001-240581, published Sept. 04, 2001. All references to Chui in this opinion are directed to the translation provided by the Examiner

As Appellants do not argue the claims separately, we focus our analysis on claim 1, and claims 2, 4-13, 19-25, 27, 28, 30, 34, 36, and 37 stand or fall with claim 1. 37 C.F.R. § 41.37 (c)(1)(iv).

### ISSUE

The Examiner takes the position that at the time the invention was made it was obvious “to employ the known macrocyclic lactone, e.g., Bryostatin 1, as the PKC [protein kinase C] activator for treating CNS [central nervous system] disorders, such as Alzheimer's disease, brain damage, both in human and in animals.” (Ans. 6.) “[T]he cited references teach[] that PKC activators with distinct structures are similarly useful for treating cognitive disorders, and the macrocyclic lactone herein, e.g., brystatin-1 is a[n] old and well-known PKC activator.” (*Id.* at 7.)

Appellants assert that the references in any combination do not “disclose or suggest use of macrocyclic lactone to improve cognitive ability, increase sAPP secretion or  $\alpha$ -secretase activity, or reduce amyloid plaques, or suggest that such use would be reasonably predictable.” (App. Br. 9.) Appellants assert that there would not be a reasonable expectation of success

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with the PTO-892 form of March 5, 2009.

<sup>2</sup> Tamura et al., JP 06279311 A, published Oct. 04, 1994.

<sup>3</sup> Pettit et al., EP 0324574 A2, published July 19, 1989.

<sup>4</sup> Ibarreta et al., *Benzolactam (BL) Enhances sAPP secretion in fibroblasts and in PC12 cells*, 10 NEUROREPORT 1035-1040 (1999).

<sup>5</sup> McGown et al., WO 96/35417, published Nov. 14, 1996.

<sup>6</sup> Driedger et al., US 6,043,270, issued Mar. 28, 2000.

in combining the references (*id.* at 24); that out of the thousands of PKC activators known there is no reasonable expectation that anyone would be suitable for the claimed methods (*id.* at 26); that the Office used hindsight reconstruction in combining the references (*id.* at 18, 31); and that “McGown teaches away from the use of bryostatin-1 as a PKC activator because McGown actually shows that the concentration of bryostatin-1 used in the combination with tamoxifen downregulates PKC (*id.* at 30).”

The issue is: Has the Examiner established by a preponderance of the evidence that the combination of references renders obvious the method of enhancing the cognitive ability of a human or animal subject by administering a macrocyclic lactone?

#### FINDINGS OF FACT

The following findings of fact (FF) are supported by a preponderance of the evidence of record.

1. Driedger is directed to producing “phorboid derivatives which variously block the toxic effects of the hydroxymethyl-containing phorboids.” (Driedger 17, ll. 11-14.) There are seven classes of phorboids contemplated by Driedger, including “a protein kinase C activator of the bryostatin class.” (*Id.* at 20, l. 43.)

[T]he non-inflammatory agonists among the compounds of this invention may be used to achieve desired physiological results such as interferon release, interleukin induction, tumor necrosis factor production, immune system stimulation and/or

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reconstitution, insulin secretion, insulinomimetic activity, acceleration of wound healing, improvement in central nervous system functions such as memory and learning and abrogation of the symptoms or progress of Alzheimer's disease, and any other application for which desirable actions of protein kinase C are found.

(*Id.* at 48, ll. 22-31; Ans. 6.)

2. Tamura disclosed a method “[t]o provide the subject activation agent having strong activation activity and expected to be useful as an agent for the treatment of senile dementia caused by central nervous lesion, especially Alzheimer's disease. . . The activation agent for protein kinase C isozyme &beta; or &gamma;.” (Tamura Abstract; Ans. 5.)

3. Chui disclosed aminobenzamide derivatives having PKC activating effect.

The inventive compound and a pharmaceutically acceptable salt thereof that can be represented by formula (I) can be effectively used orally or parent[erally administered to warm-blooded animals (e.g., humans, rabbits, guinea pigs, rats, dogs and cats) as a preventive/therapeutic agent for PKC-related diseases, such as ocular hypertension, glaucoma, central nervous system disorder, senility, Alzheimer's disease and tumors, and as an immunity activation agent by the superoxide from neutrophil cells.

(Chui ¶ 0132; Ans. 5.)

4. Petti disclosed “immunoenhancing properties of a novel series of protein kinase C activators selected from the bryostatin family.” (Petti 6, ll. 30-31; Ans. 5, 8.)

5. McGown disclosed the use of bryostatin for treating ovarian carcinoma in a patient. (McGown 21, ll. 1-15; Ans. 5.)

6. Ibarreta disclosed the use of benzolactam and LQ12, a smaller analog of benzolactam (Ibarreta 1036, see Fig 1), for their ability to induce secretion of sAPP (non-amyloidogenic soluble amyloid precursor protein) in PC-12 cells (*Id.* at 1039, see Fig 1). The results show:

Novel PKC activators cause increased secretion of non-amyloidogenic sAPP in AD fibroblasts and PC12 cells. This elevated sAPP secretion may be also accompanied by a reduction of amyloidogenic fragments. These results further indicate a key role for PKC in APP processing and, therefore, in AD pathophysiology. The study also suggests that PKC may be a useful target for preventing or slowing the pathophysiological process in AD.

(*Id.* at 1040.)

7. The Specification shows testing bryostatin in non-diseased rats for their learning ability:

The effect of PKC activators on cognition was demonstrated by the Morris Water Maze paradigm. In the present example, rats were injected intraventricularly with bryostatin-1 and trained for 4 days (following standard protocols). Retention was assessed on the 5th day. Learning was measured as the reduction of escape latency from trial to trial, which was significantly lower in the treated animals.

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Acquisition of memory was measured as time spent in the relevant quadrant (5th day).

(Spec. 22, ll. 21-25.) The results showed that bryostatin improved the cognitive ability in non-diseased rats (*id.* at 6, l. 1).

#### PRINCIPLES OF LAW

“Obviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success.” *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). The presence of a reasonable expectation of success is measured from the perspective of a person of ordinary skill in the art at the time the invention was made. *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000).

#### ANALYSIS

The claims are directed at “enhancing the cognitive ability” in a human or animal subject by administering a macrocyclic lactone. The Specification provides that “[c]ognition can be generally described as including at least three different components: attention, learning, and memory.” (Spec. 1, ll. 11-12.) Thus, improving any one of attention, learning or memory would be encompassed by the limitation “enhancing the cognitive ability” in a human or animal subject.

We are not persuaded by Appellants’ argument. We agree with the Examiner that it would have been *prima facie* obvious to administer

macrocyclic lactones to a subject in order to improve attention, learning or memory. The Examiner finds that Driedger disclosed PKC activators for treating human and animal diseases (Ans. 6). Specifically, Driedger disclosed “improvement in central nervous system functions such as memory and learning and abrogation of the symptoms or progress of Alzheimer's disease” (FF1) by using non-inflammatory agonists, which encompasses bryostatinoids (FF1). The Examiner found that Chui disclosed “PKC activators are particularly useful for treating CNS disorders, dementia or Alzheimer's disease” (Ans. 5), while Tamura disclosed “PKC activators are useful for treating senile dementia accompanied central nerve disorders, such as Alzheimer's disease.” (*Id.*) The Examiner relied on Pettit and McGown for the fact that “bryostatin and neristatin are old and well known PKC activators.” (*Id.*) The Examiner concludes that based on the combined teachings it would have been obvious “to employ the known macro cyclic lactone, e.g., Bryostatin 1, as the PKC activator for treating CNS disorders, such as Alzheimer's disease, brain damage, both in human and in animals.” (*Id.* at 6.) The evidence supports that conclusion.

We are not persuaded by Appellants’ argument that “Driedger discloses modified derivatives of macrocyclic lactones but does not even show that these derivatives have any effect on PKC activation, much less enhancing cognition.” (App. Br. 22-23.) We agree with the Examiner’s finding that Driedger disclosed that the anti-inflammatory agonist achieves improvement in central nervous system function such as memory and

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learning (FF1). There is no requirement that every embodiment disclosed within a reference must be reduced to practice. “[A] presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled.” *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003).

Driedger disclosed modified phorboid compounds that can be administered to humans and animals (Driedger col. 48, ll 48-50). As recognized by the Examiner, the modified non-inflammatory agonist compounds, that include modified phorboids of the bryostatin class, may be used to achieve the desired result of improving central nervous system function such as memory and learning (FF1). The Specification shows healthy rats treated with bryostatin have improved cognition as measured by learning a water maze (FF7). Thus, the Specification has now demonstrated, what was already known and disclosed in the art (FF1), that memory and learning can be improved by administering a non-inflammatory agonist of PKC. “Scientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention.” *Pharma Stem Therpeutic, Inc. v. ViaCell, Inc.* 491 F.3d 1342, 1364 (2007).

We are also not persuaded by Appellants’ argument that references are non-analogous art and that “[t]here is no structural similarity, whatsoever, between macrocyclic lactones and the Choi or Tamura compounds, and none of the secondary references suggest use of a

macrocyclic lactone for use in any of the claimed methods.” (App. Br. 28.) Here, each reference is pertinent either to showing the effect of a compound on PKC activation (FFs 1-6), specifically, bryostatin (FFs 4 and 5), that increasing PKC activity would be desirable for the treatment of Alzheimer’s (FFs 1-3, 6), and that memory and learning can be improved by administering non-inflammatory PKC agonist (FF1) that include bryostainoids (Driedger col. 17, l. 36). *See In re Clay*, 966 F.2d 656, 658-9 (Fed. Cir. 1992) (prior art is analogous when (1) it is from the same field of endeavor, regardless of the problem addressed, or (2) if not within the field of the inventor's endeavor, if it still is reasonably pertinent to the particular problem with which the inventor is involved.)

We conclude that the preponderance of the evidence of record supports the Examiner’s conclusion that the combination Chui or Tamura in view of Pettit, McGown, Ibarreta, and Driedger renders obvious the method of enhancing cognitive ability in a human or animal subject by administering macrocyclic lactone of claim 1. We thus affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as being obvious. As claims 2, 4-13, 19-25, 27, 28, 30, 34, 36, and 37 fall with claim 1, we affirm the rejection as to those claims as well.

#### SUMMARY

We affirm the rejection of claims 1, 2, 4-13, 19-25, 27, 28, 30, and 34-37 on the ground of nonstatutory obviousness-type double patenting as being

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unpatentable over claims 1-6 of U.S. Patent No. 6,825,229.

We affirm the rejection of claims 1, 2, 4-13, 19-25, 27, 28, 30, and 34-37 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12-61 of copending Application No. 10/937,509.

We affirm the rejection of claims 1, 2, 4-13, 19-25, 27, 28, 30, and 34-37 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 104-133 of copending Application No. 11/802,842.

We affirm the rejection of claims 1, 2, 4-13, 19-25, 27, 28, 30, 34, 36, and 37 under 35 U.S.C. § 103(a) as unpatentable over Chui or Tamura, in view of Pettit, McGown, Ibarreta, and Driedger.

#### 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

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