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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte RICHARD J. WURTMAN and INGRID RICHARDSON[1]

Appeal 2017-001454
Application 11/920,914
Technology Center 1600

Before ERIC B. GRIMES, ULRIKE W. JENKS, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for increasing the amount of synaptic membrane or increasing the size or number of synapses in a subject, which have been rejected for obviousness and obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse the rejection for obviousness and affirm the provisional rejection for obviousness-type double patenting.

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[1] Appellants identify the Real Parties in Interest as the Massachusetts Institute of Technology and Back Bay Scientific LLC. (Br. 1.).

STATEMENT OF THE CASE

The Specification states that the

> invention provides methods of increasing or enhancing the synthesis and levels of phospholipids, synapses, synaptic proteins, and synaptic membranes by a neural cell or brain cell; methods of treating a subject with a memory disorder, memory impairment, neurological disorder, or brain disease or disorder, comprising administering to the subject a composition comprising an omega-3 fatty acid, an omega-6 fatty acid, uridine, a metabolic precursor thereof, or a combination thereof.

(Spec. ¶ 3.) The Specification also states that "any of the methods and compositions of the present invention comprises administration of an omega-6 fatty acid, an omega-3 fatty acid, a uridine, and a choline salt." (*Id.* ¶ 22.)

Claims 49, 50, 52–59, 61–64, 66–73, 75, and 76 are on appeal. Claims 49 and 63 are the independent claims and read as follows:

49. A method of increasing an amount of a synaptic membrane of a neural cell or brain cell of a subject comprising

administering to said subject in need of such treatment a therapeutically effective amount of a composition having:

(a) an omega-3 fatty acid, an omega-6 fatty acid, or a combination thereof;

(b) uridine, an acyl derivative thereof, a uridine phosphate or a CDP-choline; and

(c) a choline salt,

wherein uridine, an acyl derivative thereof, a uridine phosphate or CDP-choline is dosed to provide a range of 10 to 500 mg of uridine per day and choline is dosed in a range of 100 mg to 10 g per day.

63. A method of increasing a size or number of synapses in a brain of a subject, comprising

administering to said subject in need of such treatment a therapeutically effective amount of a composition comprising

(a) an omega-3 fatty acid, an omega-6 fatty acid, or a combination thereof;

(b) uridine, an acyl derivative thereof, a uridine phosphate or a CDP-choline, and

(c) a choline salt,

wherein uridine, an acyl derivative thereof, a uridine phosphate or CDP-choline is dosed to provide a range of 10 to 500 mg of uridine per day and choline is dosed in a range of 100 mg to 10 g per day.

The claims stand rejected as follows:

Claims 49, 50, 52–59, 61–64, 66–73, 75, and 76, provisionally, for obviousness-type double patenting based on claims 74–90 of U.S. Patent application 11/920,915 (Ans. 6) and

Claims 49, 50, 52–54, 56–59, 61–64, 66–68, 70–73, 75, and 76 under 35 U.S.C. § 103(a) as obvious in view of Renshaw,[2] Merck,[3] Watkins,[4] and Eastwood[5] (Ans. 2).

I

The Examiner has provisionally rejected all of the claims on appeal for obviousness-type double patenting on the basis that they are not patentably distinct from the claims in application 11/920,915. (Ans. 6.) Appellants state that they "will file a terminal disclaimer upon allowance of

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[2] Renshaw, WO 2005/086619 A2, published Sept. 22, 2005.

[3] *The Merck Manual of Diagnosis and Therapy* 1382–83, 1393–1400 (Mark H. Beers, et al. eds., 17th ed. 1999).

[4] Watkins, US 6,989,376 B2, issued Jan. 24, 2006.

[5] Sharon L. Eastwood & Paul J. Harrison, *Synaptic Pathology in the Anterior Cingulate Cortex in Schizophrenia and Mood Disorders. A Review and a Western Blot Study of Synaptophysin, GAP-43 and the Complexins*, 55 BRAIN RES. BULL. 569–578 (2001).

claims in one of the copending applications." (Br. 4.) Because Appellants do not dispute the merits of the provisional obviousness-type double patenting rejection, we affirm it.

II

The Examiner has rejected claims 49, 50, 52–54, 56–59, 61–64, 66–68, 70–73, 75, and 76 as obvious in view of Renshaw, Merck, Watkins, and Eastwood (Ans. 2). The Examiner finds that Renshaw discloses treating depression by "administering to a subject various cytosine and uridine compounds, and an omega-3 fatty acid." (*Id.* at 3.) "In one embodiment the subject has a co-morbid neurological disease," such as Alzheimer's disease. (*Id.*) The Examiner finds that Renshaw does not disclose the dosages recited in the claims on appeal, and also does not disclose administering a choline salt. (*Id.*)

The Examiner finds that "Merck discloses that depressed patients may have cognitive impairment that resembles dementia, including memory loss," that "depression often coexists in patients suffering from dementia," and that causes of dementia include Alzheimer's disease. (*Id.*) The Examiner finds that Watkins discloses a method of treating Alzheimer's disease or depression by administering uridine and choline salts (*id.* at 3–4) and Eastwood discloses that subjects suffering from psychiatric disorders have decreased synaptic density of excitatory synapses (*id.* at 4).

The Examiner concludes that it would have been obvious to use Renshaw's method "to treat depressed patients having cognitive or memory impairment secondary to depression . . . because Merck discloses that dementia can be a symptom of an underlying depression." (*Id.*) The

Examiner also concludes that it would have been obvious "to add choline stearate or choline bitartrate to the compositions administered in the method of Renshaw. . . because Watkins et al. discloses that these choline compounds are useful in combination with uridine compounds for treating depression." (*Id.*)

> Alternatively, the Examiner reasons that it would have been obvious to administer the therapy described by Watkins et al. to a patient suffering from dementia, and then additionally if the patient develops depression secondary to dementia as described by Merck, to administer a prior art treatment for depression, such as the therapy described by Renshaw et al., as Merck discloses that patients suffering from dementia are at risk for depression and can be treated with conventional therapies for depression.

(*Id.* at 5.)

Appellants argue, among other things, that "the application contains several examples with experimental results that distinguish the recited combination from the prior art. In particular, the examples' experimental results demonstrate the unexpected synergistic effect of combining the recited ingredients." (Br. 24.) Appellants point to the Specification's Example 5 as providing evidence that the combination of choline, uridine, and an omega-3 fatty acid (DHA) acts synergistically to increase the synaptic membrane in the brains of gerbils. (*Id.*) Appellants point to the Specification's Example 6 as evidence that these same gerbils had increased brain phospholipid levels, and that administration of both UMP and DHA along with a standard diet containing choline "increased all of the phospholipids by more than the sum of the increases produced by UMP or DHA alone." (*Id.* at 24–25.) Finally, Appellants point to the Specification's Example 7 as evidence that gerbils administered a combination of choline,

uridine, and DHA had increased levels of synaptic proteins in their brains. (*Id.* at 25.)

We agree with Appellants that the evidence of unexpected results is sufficient to demonstrate the nonobviousness of the claimed methods. The Specification's Example 5 describes an experiment in which gerbils were fed a "[c]ontrol standard diet (Table 4) . . . which contained 0.1% choline chloride (CC), corresponding to a daily dose of 50 mg/kg/day." (Spec. ¶ 238.) Groups of gerbils were fed the control diet alone or supplemented with either or both of UMP and DHA. (*Id.* ¶ 244.) The Specification states that DHA increased phospholipid levels significantly above the control group, and "[c]ombination of DHA with UMP resulted in a further increase (26%) that was synergistic (i.e. greater than the sum of the increases observed in the DHA (12%) and UMP (5%) groups)." (*Id.* ¶ 245.)

The Specification's Example 6 likewise states that, in the gerbils from Example 5 (*id.* ¶ 252), "UMP + DHA increased all of the phospholipids by more than the sum of the increases produced by UMP or DHA alone." (*Id.* ¶ 253.) The Specification's Example 7 states that "[b]rain levels of 4 synaptic proteins were measured in [gerbils] receiving both UMP and DHA in the amounts described in Example 5." (*Id.* ¶ 259.) The Specification states that the levels of all four proteins increased after three or four weeks of treatment (*id.*) and that "[t]hese findings provide further evidence that administration of PUFA [polyunsaturated fatty acid] and uridine increases the quantity of synaptic membranes. These increases were similar to those observed in phospholipid levels, showing that synapse levels were increased in the brain." (*Id.* ¶ 260.)

The Examiner provides no evidence showing that a person of ordinary skill in the art would have expected synergism between UMP and DHA, when administered with a control diet containing choline, in their effects on brain phospholipid levels, the quantity of synaptic membranes, or synapse levels. Rather, the Examiner reasons that "the cited prior art describes a combination of an omega-3 fatty acid and uridine, (Renshaw) and a combination of choline and uridine. (Watkins) In order to overcome a *prima facie* case of obviousness, the unexpected results must relate to the difference between the claims and the prior art." (Ans. 15–16.) The Examiner concludes that

> [s]ince Renshaw et al. already discloses administering uridine compounds and omega fatty acids together, showing a synergistic interaction between UMP and DHA does not overcome the finding of obviousness. Examples 5-10 in the specification, which Appellant also points to, also specifically concern the interaction between UMP and DHA. Therefore Appellant has not demonstrated unexpected results which could overcome the *Prima facie* finding of obviousness.

(*Id.* at 16.)

We disagree. Evidence of unexpected results must show a comparison to the closest prior art. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."). However, the comparison that is required is to an embodiment that actually exists in the prior art; requiring a comparison to an embodiment that is merely made obvious by the prior art "would amount to requiring comparison of the results of the invention with

the results of the invention." *In re Chapman*, 357 F.2d 418, 422 (CCPA 1966).

> In this case, Watkins states that one of the objects of its invention is to establish a synergy between uridine and various compounds affecting cholinergic pathway and/or phospholipid metabolism. Among them are CDP-choline, choline, choline salts, lecithin or phosphatidylcholine, phosphatidylethanolamine, various fatty acids, e.g., linoleic acid, and other known in the art compounds or mixtures thereof involved in phospholipid synthesis.

(Watkins 5:19–24.) "More specifically choline-based compounds are contemplated as compounds acting in synergy with uridine or uridine source. Among them are choline, choline salts or esters, such as choline bitartrate or stearate or the like, or compound[s] that dissociate to choline." (*Id.* at 5:60–64.) Watkins, however, does not provide any working examples showing evidence of synergy between uridine and any other compound; all of the examples provided by Watkins are prophetic. (*Id.* at 6:11 to 9:16.)

Renshaw discloses the combination of uridine, administered by injection, and omega-3 fatty acids, administered as a dietary supplement, in a rat model of depression. (Renshaw 30:19–25, 31:20–25.) Renshaw states that uridine alone had effects similar to those seen after treatment with standard antidepressants. (*Id.* at 36:1–8.) Renshaw states that omega-3 fatty acids alone also had effects similar to those seen after treatment with standard antidepressants, but only after treatment for thirty days. (*Id.* at 36:10–22.) Renshaw states that, when a sub-effective dose of uridine was administered to rats receiving a normally sub-effective dose of omega-3 fatty acids for ten days, the combination reduced immobility and increased both swimming and climbing, effects similar to those of uridine alone or

omega-3 fatty acids alone. (*Id.* at 36:25 to 37:9.) Renshaw does not, however, state that the effects of combining uridine and omega-3 fatty acids were more than additive or synergistic.

Thus, the closest embodiment that actually existed in the prior art states that the combination of uridine and omega-3 fatty acids was more effective than either agent alone in treating depression. However, the Examiner has not pointed to evidence showing that a person of ordinary skill in the art would have expected the three-component mixture recited in the claims (e.g., an omega-3 fatty acid, uridine, and a choline salt) to show synergism in increasing the amount of synaptic membrane, or increasing the size or number of synapses in a subject, compared to the combination of choline with uridine or the combination of choline with an omega-3 fatty acid.

Because Appellants have provided evidence that the claimed methods provide results that are unexpectedly superior to the closest prior are, we reverse the rejection of claims 49, 50, 52–54, 56–59, 61–64, 66–68, 70–73, 75, and 76 under 35 U.S.C. § 103(a) based on Renshaw, Merck, Watkins, and Eastwood.

SUMMARY

We affirm the provisional rejection for obviousness-type double patenting.

We reverse the rejection under 35 U.S.C. § 103(a) based on Renshaw, Merck, Watkins, and Eastwood.

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