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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte PATRICK JOSEPH GERARDUS HENDRIKUS KAMPHUIS, MARTINE GROENENDIJK, and ANKE BONGERS[1]

Appeal 2018-007214
Application 12/666,611
Technology Center 1600

Before DEBORAH KATZ, JOHN G. NEW, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party-in-interest as N.V. Nurtricia. App. Br. 3.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 18, 20, 26, 27, and 31–35. Specifically, the claims stand rejected as unpatentable under 35 U.S.C. § 103(a) as being obvious over the combination of Wurtman et al. (WO 2006/127620 A2, November 30, 2006) ("Wurtman"), P. Quadri et al., *Homocysteine, Folate, and Vitamin B-12 in Mild Cognitive Impairment, Alzheimer Disease, and Vascular Dementia*, 80 AM. J. CLIN. NUTR. 114–22 (2004) ("Quadri"), and M.F. Folstein et al., *"Mini-Mental State" A Practical Method for Grading the Cognitive State of Patients for the Clinician*, 12 J. PSYCHIATR. RES., 189–98 (1975) ("Folstein").

Claims 18, 20, 26, 27, and 31–35 also stand rejected as unpatentable under 35 U.S.C. § 103(a) as being obvious over the combination of Wurtman, Folstein, and J.A. Luchsinger et al., *Dietary Factors and Alzheimer's Disease*, 3 THE LANCET NEUROL. 579–87 (2004) ("Luchsinger").

Claims 18 and 33 stand rejected as unpatentable under the nonstatutory doctrine of obviousness-type double patenting over claims 1, 4, 6 & 11 of US 8,361,989 (the "'989 patent").[2]

We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[2] Appellant requests that the Examiner's rejection on this ground be held in abeyance pending determination that the claims are otherwise allowable. We consequently summarily affirm the Examiner's rejection upon this ground. *See* 37 C.F.R. § 41.37(c)(iv) ("[A]ny arguments or authorities not included in the appeal brief will be refused consideration by the Board for purposes of the present appeal").

NATURE OF THE CLAIMED INVENTION

Appellant's invention is directed to the use of a composition comprising: (a) uridine or uridine phosphate; and (b) docosahexaenoic acid and/or eicosapentaenoic acid, for improving memory and/or the treatment or prevention of impaired memory function, in a subject with a mini-mental state examination of 24–26, wherein said composition is enterally administered to the subject. Abstr.

REPRESENTATIVE CLAIM

Claim 18 is representative of the claims on appeal and recites:

> 18. A method for improving delayed recall and/or memory function of a human subject with a mini-mental state examination of 24–26, comprising enterally administering to the subject a composition comprising:
>
> a. 0.1–2 g uridine or uridine phosphate, calculated as uridine monophosphate, per daily dosage unit;
>
> b. 400–5000 mg of the sum of docosahexaenoic acid and eicosapentaenoic acid per daily dosage unit; and
>
> c. vitamin E, vitamin C, vitamin B 12, vitamin B6 and folic acid, wherein 1.5–5 μg vitamin B12 and 150–750 μg folic acid is administered per day.

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App. Br. 11.

ISSUES AND ANALYSES

We agree with, and expressly adopt, the Examiner's findings, reasoning, and conclusion that the claims are *prima facie* obvious. We address below the arguments raised by Appellant.

Issue 1

Appellant argues that the combined cited prior art neither teaches nor suggests all the claimed ingredients in the amounts required. App. Br. 4.

Analysis

The Examiner finds that Wurtman teaches a method of improving memory disorder or impairment (including a mini-mental state examination of 24–26; see Appellant's Spec. 1, 19) by enterally administering a composition comprising uridine phosphate and the omega-3 fatty acid docosahexaenoic acid ("DHA") and/or the omega-6 fatty acid eicosapentaenoic acid ("EPA"). Non-Final Act. 7, filed April 4, 2016 (citing, e.g., Wurtman 2, 9, 12–13, 29, 46) as it relates to claims 18(a) & (b). The Examiner finds that Wurtman teaches that its compositions comprise 100–500 mg/day uridine and 400–3000 mg/day of DHA or EPA, and choline. *Id.* The Examiner also finds that Wurtman teaches the use of the mini-mental test as another embodiment of their invention to assess improvement of cognitive function. *Id.* (citing Wurtman 19).

The Examiner finds that Folstein teach a "simplified, scored form of the mental status examination, the mini-mental state (MMS)," which requires only 5–10 minutes to administer, as a means of assessing cognition and delayed recall function. Non-Final Act. 9 (citing Folstein 189–90, 193).

The Examiner finds Quadri teaches that folate and vitamin B12 & B6 deficiencies may precede Alzheimer's disease/cognitive decline and, therefore, additional dietary intake of these nutritional factors may be beneficial to improve cognition. Non-Final Act. 9–10 (citing Quadri 114, 115, Table 2).

The Examiner concludes that it would have been obvious to one of ordinary skill to supplement Wurtman's method of improving cognition and neurological functions with uridine, DHA, EPA, and choline, with Quadri's folate, and vitamins B12 and B6. Non-Final Act. 9. The Examiner concludes that a person of ordinary skill would be motivated to combine the references, because they each teach compositions beneficial in treating cognitive impairments in patients beginning to experience cognitive deficiencies in diseases such as Alzheimer's disease. *Id.* The Examiner further concludes that it would have been obvious to use the method of Folstein to assess cognitive improvement. *Id.* at 9–10.

Similarly, the Examiner finds that Luchsinger teaches that "high intake of vitamins C, E, B6, and B12, and folate, unsaturated fatty acids [e.g., EPA and DHA] and fish are related to a low risk of AD" (Alzheimer's disease. Non-Final Act. 12–13 (quoting Luchsinger Abstr.).

The Examiner concludes, for the same reasons cited *supra*, that it would have been obvious to a person of ordinary skill in the art to combine Wurtman's method with Luchsinger's vitamins E, C, B12, B6 and folate. Non-Final Act. 13. The Examiner concludes that a person of ordinary skill would be motivated to combine the references, because they each teach compositions beneficial in treating cognitive impairments in patients beginning to experience cognitive deficiencies in diseases such as Alzheimer's disease. *Id.*

Appellant disputes the Examiner's finding that the formulations taught by Wurtman formulation necessarily contain dietary supplements, such as phospholipids, choline, vitamins B6, B 12, E, C, folate and selenium in their recommended dietary allowances for humans. App. Br. 4–5 (citing Final

Act. 14. However, Appellant argues Wurtman's only description is of the diet (for gerbils) is provided in Table 4, which shows that the diet contains protein (16.7%), carbohydrate (60.9%), oil, fiber, ash (13.7%), choline (0.1%), saturated fatty acids (7.34 g/kg), and unsaturated fatty acids, such as C18:1n-9 oleic acid (8.96 g/kg), C18:2n-6 linoleic acid (23.12 g/kg), and C18:3n-3 linolenic acid (1.53 g/kg). *Id.* at 5 (citing Wurtman 53–54). Therefore, Appellant argues, Wurtman does not teach formulations comprising vitamins E, C, B12 and B6, and folic acid. *Id.*

Appellant argues further that, although Quadri teaches that a folic acid deficiency may precede cognitive impairment, dementia, or Alzheimer's disease, Quadri does not teach that actual supplementation with folic acid can improve or reverse such conditions. App. Br. 5. Appellant contends that the Examiner erroneously assumes that Luchsinger teaches that: "high intake of vitamins C, E, B6, and Bl2, and folate, unsaturated fatty acids ... are related to a low risk of AD … in studies of treating Alzheimer's patients." *Id.* (citing Final Act. 18 (quoting Luchsinger Abstr.)).

Appellant acknowledges that Luchsinger teaches that: "[s]ome studies suggest high intake of vitamins C, E, B6, and B12, and folate, unsaturated fatty acids, and fish are related to a low risk of AD," but Appellant asserts that the Examiner cannot dismiss that Luchsinger acknowledges that the "reports are inconsistent." App. Br. 5 (quoting Luchsinger Abstr.). Appellant argues that Luchsinger consistently mentions the conflicting data with regards to dietary factors/supplements: for instance, with respect to vitamin C, Luchsinger mentions one study in which: "4000 people age 65 years and older found that a combination of supplements of vitamins C and E, but not supplements of individual antioxidants, was associated with a low

risk of AD." *Id.* (quoting Luchsinger 580). Similarly, argues Appellant, Luchsinger cites another study in which: "5395 people age 55 years and older found that dietary intake of vitamins E and C, but not supplement intake, was associated with a low risk of AD." *Id.* at 5–6. With regard to vitamins B12, B6, and folate, Appellant notes that Luchsinger states that "the data relating vitamins B12, B6, and folate to cognitive decline and AD are inconsistent" and concludes by stating that "[m]ost of the data relating diet and AD are from observational studies and are inconsistent. Thus, recommendations of dietary interventions specifically for the prevention of AD cannot be made at this time." *Id.* (quoting Luchsinger 585, left column).

Therefore, argues Appellant, even if Luchsinger could have been interpreted as suggesting the use of vitamins E, B6, and B12, and folic acid, the studies summarized in Luchsinger are conflicting at best. App. Br. 6. Furthermore, Appellant argues, the recommended doses for vitamin B12 and folate suggested by Luchsinger (0–4 mg of vitamin B12 and 2–5 mg of folate) are much greater than the ranges recited in the claims (1.5–5 μg vitamin B12 and 150-750 μg folic acid). *Id.* Consequently, Appellant argues, Luchsinger not only fails complement the deficiencies of Wurtman, it also fails to provide any reasonable motivation to combine any of the "recommended" vitamins/supplements with uridine monophosphate, DHA and/or EPA for treatment of the populations claimed, because Luchsinger does not provide any assurance of a reasonable expectation of success. *Id.*

Despite the fact that Appellant argues both of the Examiner's rejections together, we are persuaded by Appellant with respect to the Examiner's rejection over the combination of Wurtman, Quadri, and Folstein. Quadri is directed to the relationship between elevated plasma

homocysteine levels caused by decreased vitamin B6, B12, and folic acid, and the onset of vascular dementia and Alzheimer's disease. *See* Quadri Abstr., 118. Quadri is silent, however, with respect to EPA, DHA, uridine, and the antioxidant vitamins C and E. Wurtman teaches administration of EPA and/or DHA and uridine in treating mild or early stages of dementia (which, as the Examiner finds) could be reasonably interpreted as corresponding to a mini-mental examination state of 24–26), but is silent with respect to vitamins C, E, B6, B12, or folic acid. *See, e.g.*, Wurtman 2.

The Examiner attempts to remedy this deficiency by pointing to, *inter alia*, paragraph [0199] of Wurtman, which teaches:

> "Pharmaceutical composition" refers, in another embodiment, to a dietary supplement. In another embodiment, the term refers to a *nutritional supplement*. In another embodiment, the term refers to a foodstuff of any sort that has been enriched with an omega-3 fatty acid. In another embodiment, the term refers to a foodstuff that has been enriched with an omega-6 fatty acid. In another embodiment, the term refers to a foodstuff that has been enriched with a uridine. In another embodiment, the term refers to a foodstuff that has been enriched with a choline. In another embodiment, the term refers to a foodstuff that has been enriched with a choline salt.

(Emphasis added). The Examiner finds that this teaching, and especially the teaching of a nutritional supplement, necessarily include the minimum daily requirements of the missing vitamins. However, without more evidence to expressly support this determination, we determine that this conclusory finding by the Examiner lacks sufficient evidentiary support to show that Wurtman teaches the inclusion of vitamins C, E, B6, B12, or folic acid as recited in the claims.

Consequently, because neither Wurtman, Quadri nor Folstein teach or suggest the administration of antioxidant vitamins C or E to human patients with a mini-mental state examination of 24–26, we reverse the Examiner's rejection upon that ground.

With respect to the Examiner's rejection of the claims over Wurtman, Folstein, and Luchsinger, Luchsinger teaches that:

> Most of the data relating diet and AD are from observational studies and are inconsistent. Thus, recommendations of dietary interventions specifically for the prevention of AD cannot be made at this time. However, some of the diets that may be beneficial for AD are beneficial for other disorders, such as cardiovascular disease, or are unlikely to be harmful, and some recommendations can be made on the basis of these characteristics.
> ….
> There are conflicting data relating antioxidant intake to risk of cardiovascular outcomes and AD. However, in light of the relative safety of vitamin E and the results of the only trial of vitamin E supplementation with 2000 IU a day, it may be seen as a benign measure that is not proven in trials of primary prevention. The intake of multivitamins may be recommended given the potential benefits from their content of folate and B vitamins and the proven benefits of supplementation of other nutrients, such as calcium and vitamin D for osteoporosis.… It may be advisable to supplement with at least 4 mg of folic acid, 2 mg of vitamin B6, and 6 μg of vitamin B 12, and increase the doses according to homocysteine response, up to the doses currently used in clinical trials (25 mg of vitamin B6, 0.4 mg of vitamin B12, and 2.5 mg of folate).
>
> There is some evidence to suggest that intake of macronutrients, such as saturated fats, is related to AD, and that caloric restriction may prevent AD and other ageing related disorders…. A diet low in saturated and trans fatty acids and high in monounsaturated, polyunsaturated, and fish-related fats seems to prevent cardiovascular disease. These observations may be extrapolated

> to the prevention of cognitive problems awaiting the results of randomised trials specific to cognition.

Luchsinger 585 (internal references omitted).

Luchsinger, a review article, thus teaches that, although the results of different studies have provided some inconsistent results and, in the case of polyunsaturated fatty acids, awaits further testing, there are generally positive results and further testing is encouraged. We do not agree with Appellant that the teachings of Luchsinger are such that the expectation of success by a person of ordinary skill in the art in combining the references as claimed would be *prima facie* unreasonable. This is particularly true in view of the teachings of Wurtman that EPA and/or DHA and uridine are effective in treating early or mild stages of dementia. *See In re Longi*, 795 F.2d 887, 897 (Fed. Cir. 1985) (holding that "[o]nly a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness.").

Finally, with respect to dosages, Luchsinger teaches administration of folate at dosages of 2.5–4 mg and B12 at 6–400 μg. Luchsinger 585. Claim 18 recites daily dosages of 150–750 μg folate and 1.5-5 μg. We acknowledge that there is some distance between the prescribed dosages of Luchsinger and the claims, however:

> The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. These cases have consistently held that in such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range.

In re Woodruff, 919 F. 2d 1575, 1578 (Fed. Cir. 1990). We address Appellant's argument concerning unexpected results *infra*. However,

Appellant does not argue that the range of folic acid and vitamin B 12 recited in the claim is critical to its function or, more importantly, that higher dosages, though still within the usual range (as taught by Luchsinger 585), would not achieve the same or similar results. We are therefore not persuaded by Appellant's arguments with respect to this rejection.

Issue 2

Appellant argues that the Examiner erred because cone of the cited prior art references teach treatment of "a human subject with a mini-mental state examination of 24–26." App. Br. 6.

Analysis

Appellant argues that Wurtman does not teach improving delayed recall and/or memory function in a human subject with a mini-mental state examination of 24–26. App. Br. 6. Appellant contends that the Examiner appears to have interpreted the reference to mini-mental state examination as the use of the mini-mental state examination (MMSE) for "assessing improvement of cognitive function." *Id.* (citing Final Act. 15). However, argues Appellant, claim 18's recitation of "a human subject with a mini-mental state examination of 24–26" is not in reference to a method of "assessing improvement of cognitive function," but rather a characterization of a specific human subject population that is to be administered the compositions recited. *Id.*

Appellant contends that, although Wurtman teaches administering its compositions to subjects with Alzheimer's disease, the disease may be in the early, mild, or late stage, and the stage of Alzheimer's can be assessed using

the Functional Assessing Staging ("FAST") scale. App. Br. 7. Appellant contends that the inventors of the claims on appeal have discovered that, "within the group of 20–26, the memory impairment in the sub-group of 24–26 may even be reversible, as the pathological pathways have just started to develop." *Id.* (quoting Spec. 1–2). Appellant asserts that the inventors then learned that compositions comprising uridine or uridine phosphate, DHA and/or EPA, vitamins E, C, B12 and B6, and folic acid would be particularly beneficial in subjects having a MMSE score of 24–26, which is nowhere suggested by Wurtman. *Id.*

Appellant therefore contends that, because of the unpredictable and conflicting state of the art, a person of ordinary skill in that art would not have a reasonable expectation of success of improving delayed recall and/or memory function in a human subject with a MMSE score of 24–26 by administering a composition comprising uridine or uridine phosphate, DHA and/or EPA, and vitamins E, C, B12 and B6, and folic acid. App. Br. 7.

We are not persuaded by Appellant's argument. Wurtman expressly teaches that:

> This 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.

Wurtman ¶ 1. Furthermore, Wurtman teaches that: "In another embodiment, the Alzheimer's disease is at an early stage. In another embodiment, the Alzheimer's disease is at a mild stage." *Id.* at ¶ 79; *see also* claim 14.

> Appellant's Specification discloses that:
>
> In the MMSE test, any score of 27 or higher (out of 30) is effectively normal. In the patients with dementia, 20–26 indicates mild dementia, 10–19 moderate dementia, and below 10 severe dementia.
> ….
>
> The subgroup of subjects with a MMSE score of 24 to 26 comprises two populations. Firstly, it comprises those subjects who do not receive medication for memory impairment, i.e. the drug naive subjects. The treatment of this subgroup is particularly preferred as in these subjects the balance between side effects and benefits of pharmaceutical intervention is still negative.….
>
> Secondly, the subgroup of subjects with a MMSE score of 24 to 26 comprises a population of *subjects with a very mild form of Alzheimer's Disease*. Memory improvement through nutritional therapy is particularly desired in subjects with a very mild form of Alzheimer's Disease. If improvement of memory function could be achieved pharmaceutical intervention could be reduced or even postponed if significant improvements are observed.

Spec. 1–2 (emphasis added). Appellant's Specification thus teaches that "human subject[s] with a mini-mental state examination of 24-26" include those suffering from a very mild form of Alzheimer's disease, which corresponds to Wurtman's teaching that its compositions can be administered to individuals with an early or mild stage of Alzheimer's disease. Wurtman ¶ 79; *see also* claim 14. We acknowledge that Wurtman does not teach administration of folic acid, vitamins C, E, B6, or B12, but the Examiner relies upon the teachings of Luchsinger as teaching those, as well as polyunsaturated fatty acids such as DHA or EPA. *See* Luchsinger 582–83. We therefore do not find Appellant's arguments persuasive with respect to this issue.

Issue 3

Appellant argues that their unexpected results are sufficient to overcome the Examiner's *prima facie* conclusion of obviousness. App. Br. 7.

Analysis

Appellant argues that the inventors discovered an effect of B-vitamins (i.e., vitamins B6 and Bl2 and folic acid) in the presence of antioxidants (i.e., vitamins C and E), polyunsaturated acids ("PUFA," i.e., EPA and DHA), and uridine monophosphate ("UMP") on improving delayed recall and/or memory function of a human subject with a mini-mental state examination of 24–26. App. Br. 7. However, Appellants assert that they have also discovered an unexpected synergistic effect. *Id.*

In support of this contention, Appellant presents data showing that a combination of PUFAs, UMP, and antioxidants increases cholinergic M1 receptor activity in PC12 cells by approximately 25% over baseline levels. App. Br. 8.[3] However, Appellant explains, if B-vitamins are added to the combination, the activity rises to 45% over baseline, well above the additional 5% contribution expected of B-vitamins alone. *Id.* In support of this argument, Appellant points to the Declaration of Dr. Laus Broersen,

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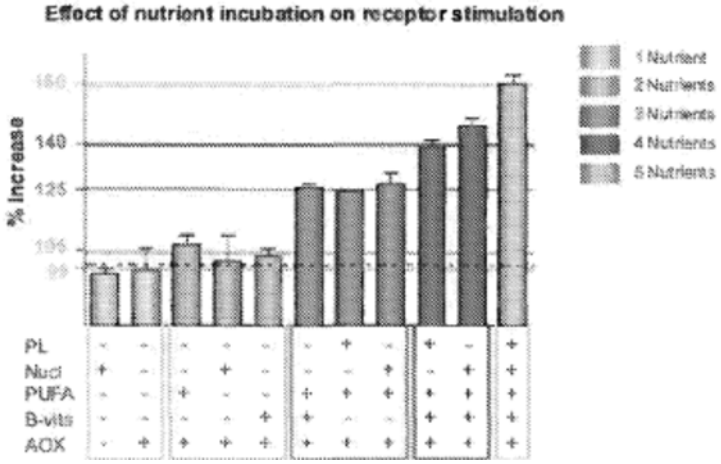
[3] Appellant states that this data was presented at the 12th Congress of the EFNS (25 August 2008, Madrid, Spain) (of record), and that a similar study was subsequently published as PJ. Savelkoul et al., *A Specific Multi-Nutrient Formulation Enhances M1 Muscarinic Acetylcholine Receptor Responses in vitro*, 120 J. NEUROCHEM. 631–40 (2012).

filed July 6, 2017 (the "Broersen Declaration"). In his Declaration, Dr. Broersen presents the data depicted below:



The data depicted in the Broersen Declaration demonstrates the effect on M1 receptor response of incubation of PC12 cells with various nutrient solutions

Appellant disputes the Examiner's findings that synergism should be based on the raw percentages of M1 receptor activity and that the data therefore fail to demonstrate synergy. App. Br. 8. However, Appellant contends, the Examiner's method for calculating synergism fails to discount the baseline activity. *Id.* And, Appellant argues, because all of the combinations contain antioxidants ("AOX," i.e., vitamins C and E), the most appropriate baseline for determining the effect of the additional components would be the AOX baseline value, as indicated by the dashed line. *Id.* Therefore, contends Appellant, in determining the effect of the addition of B-vitamins (bar# 5 = AOX + B vitamins = 105%), the baseline for AOX (100%) must be subtracted (105%-100% = 5%). *Id.* at 9. Accordingly, as shown in the table below, the various combinations of B-vitamins, PUFA (i.e., EPA and DHA), and Nucl (i.e., UMP) to AOX (i.e., vitamins C and E)

are synergistic (i.e., the effect of the combination is greater than the sum of each effect taken separately).

Appellant also disputes the Examiner's finding that the data from this study on PC12 cells has "no reasonable merit in regards to 'improving delayed recall and/or memory.'" App. Br. 9 (quoting Final Act. 6). Appellant argues that the Examiner fails to recognize that the purpose for providing the PC12 cell line data is to merely provide a mechanistic basis for the improvement in delayed recall and/or memory, showing that a composition comprising the combination of UMP, DHA and/or EPA, vitamins B6, B12, C, and E and folic acid has a synergistic effect on Ml receptor activity. Appellant points to the Broersen Declaration and Examples 1 and 2 of Wurtman, PC 12 are an art-recognized model system for studying brain function. *Id.* (citing Broersen Decl. ¶¶ 13–19).

Appellant argues further that the Specification demonstrates that the compositions recited in the claims are effective in achieving the claimed method. App. Br. 9. Appellant points to Example 2 of the Specification, which summarizes a study in which groups with a MMSE of 24–26 were administered a drink with or without EPA, DHA, phospholipids, choline, UMP, vitamin E, vitamin C, selenium, vitamin B12, vitamin B6 and folic acid. *Id.* Appellant states that the outcome measured was a (delayed) verbal memory task (derived from Wechsler Memory Scale-revised, "WMS-r"). *Id.* Appellant asserts that, as shown in Example 2 and Table 1, there was a significant difference between the two groups, with the control group showing an average decline of -0.165 point and the treatment group showing an average improvement of 0.983 points. *Id.* Appellant argues that the ability of such compositions to improve delayed recall and/or memory in

subjects with MMSE of 24–26 is completely absent from the teachings of Wurtman, Folstein, Quadri, and Luchsinger. *Id.* at 9–10.

We are not persuaded by Appellant's arguments. Even if we assume, *arguendo*, that the data presented in the Figure presented in the Broersen Declaration is probative of synergy in the amplitude of M1 receptor potentials generated *in vitro* in PC12 cells exposed to the constituents of Appellant's composition, we are not persuaded that the nexus between the synergy observed in the PC12 cell receptor potentials *in vitro* and the claimed "improve[ed] delayed recall and/or memory function" has been sufficiently established by Appellant. Synergism, in and of itself, is not conclusive evidence of non-obviousness in all instances. *See In re Kollman*, 595 F.2d 48, 55 n.6 (CCPA 1979). We acknowledge the Broersen Declaration's opinion that: "many experts in the field of neuron study routinely rely on PC 12 cells as a model for neurobiological and neurochemical studies linked to memory loss and for drawing the same conclusions made by the present inventors." *See* Broersen Decl. ¶ 14 *et seq*.

Nevertheless, although the PC12 cell *in vitro* system may serve as a useful model of neuronal function that may play a role in progressive dementia, it is a long way, in terms of explaining mechanisms and causality, from PC12 cells *in vitro* to the loss of memory and cognitive function in an intact and functioning human brain. We do not find Appellant's argument that the allegedly unexpected *in vitro* results are probative of a direct causal link between *in vitro* and *in vivo*, despite their usefulness as a model. *See In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (holding that unexpected results must also be "commensurate in scope with the degree of protection sought by the claimed subject matter").

Moreover, neither Appellant's Specification nor the Broersen Declaration demonstrate that the recited composition has an actual *synergistic* effect on "a human subject with a mini-mental state examination of 24–26," as required by the claims. We agree with Appellant that the composition does demonstrate a statistically significant effect on such patients when compared to control, but we are not persuaded that such results are unexpected or surprising in view of the teachings of the combined cited prior art. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (Unexpected results that are probative of nonobviousness are those that are "different in kind and not merely in degree from the results of the prior art") (citation omitted). We are consequently not persuaded that Appellant's evidence of unexpected results are sufficient to overcome the Examiner's *prima faci*e conclusion of obviousness. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007) ("Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion").

NEW GROUND OF REJECTION

We enter the following new ground of rejection for claims 18, 20, 26, 27, and 31–35 under the provisions of 37 CFR § 41.50(b).

Claims 18, 20, 26, 27, and 31–35 are rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Wurtman, Folstein, and Luchsinger, and Quadri. As we have explained *supra*, Quadri does not teach administration of antioxidant vitamins C or E, however Luchsinger teaches a review of studies using of those antioxidants in individuals with dementia. *See* Luchsinger 580–81.

Quadri is directed to examining the associations of plasma total homocysteine, serum folate, and vitamin B-12 concentrations with mild cognitive impairment, Alzheimer's disease, and vascular dementia, independently of other vascular and nonvascular risk factors. Quadri 115. Quadri's subjects are selected, *inter alia*, from control patients group (showing new signs of dementia) and patients defined clinically at a level of 0.5 on the Clinical Dementia Rating ("CDR"). Patients in the latter group correspond generally with the 24–26 range of the mini-mental state examination. *See* Quadri Table 1.

Quadri teaches that "[I]n this mildly cognitively impaired group [i.e., the CDR 0.5 group], the homocysteine concentration appeared to be significantly correlated with global cognitive performance, despite the narrower range of MMSE scores considered." Quadri 119. Quadri further teaches that:

> It is possible, however, to modify these putative environmental determinants of cognitive deterioration by nutrition: dietary folic acid alone or in combination with vitamin B-12 is in fact a safe, simple, and economic therapeutic strategy to effectively reduce plasma homocysteine concentrations. The adjunct of vitamin B-6 does not seem to have a significant additional effect, although each of the B vitamins might have an effect on cognition independent of their potential influence on plasma homocysteine concentrations. A homocysteine-lowering effect in AD patients has also been shown in an open-label trial of folic acid, Vitamin B-12, and vitamin B-6 regimen.

Id. at 121. Quadri thus expressly suggests that administration of vitamins B12, B6, and folate can be beneficial to patients by reducing the levels of serum homocysteine that is correlated with cognitive performance in this group.

We conclude that a person of ordinary skill in the art would have found it obvious to combine the teachings of Quadri with those of the other cited prior art references to arrive at the claimed invention. We further conclude that a person of ordinary skill in the art would have been motivated, and with a reasonable expectation of success, to combine the teachings of Quadri with those of Wurtman, Luchsinger, and Folstein (descried *supra*), to reduce the levels of serum homocysteine that is positively associated with impaired global cognitive performance of a human subject with a mini-mental state examination of 24–26.

DECISION

The Examiner's rejection of claims 18, 20, 26, 27, and 31–35 under 35 U.S.C. § 103(a) is affirmed.

We have also entered a new ground of rejection under 37 C.F.R. § 41.50(b) for claims 18, 20, 26, 27, and 31–35.

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). 37 C.F.R. § 41.50(b) provides that "[a] new ground of rejection … shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellants, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner.…

> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record.…

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

AFFIRMED

37 C.F.R. § 41.50(b)

Claims Rejected	Basis	Affirmed	Reversed	New Ground
18, 20, 26, 27, and 31–35	§ 103(a) over Wurtman, Quadri, Folstein		18, 20, 26, 27, and 31–35	
18, 20, 26, 27, and 31–35	§ 103(a) over Wurtman, Folstein, Luchsinger	18, 20, 26, 27, and 31–35		
18, 33	Obviousness-type double patenting	18, 33		
18, 20, 26, 27, and 31–35	§ 103(a) over Wurtman, Folstein, Luchsinger, Quadri			18, 20, 26, 27, and 31–35
Overall Outcome		18, 20, 26, 27, and 31–35		18, 20, 26, 27, and 31–35