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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DAVID GREENWOOD and WILFRIED DIMPFEL

Appeal 2018-004506
Application 14/307,231
Technology Center 1600

Before JEFFREY N. FREDMAN, TAWEN CHANG, and JAMIE T. WISZ, *Administrative Patent Judges.*

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 9, 10, and 15. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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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 BTG International Limited. Appeal Br. 3.

BACKGROUND

The Specification explains that "[i]t is known that both acute and chronic neurodegenerative states in mammals . . . can be treated by inducing ketosis." Spec. 1:12–13. The Specification further explains that "ketosis can be provided by restriction of diet . . . or by administration of ketogenic materials, such as triglycerides, free fatty acids, alcohols (eg butan-1, 3-diol), acetoacetate and [(*R*)]-3-hydroxybutyrate and their conjugates with each other and further moieties, eg. esters and polymers of these." *Id.* at 1:13–17.

According to the Specification, "[t]he present inventors . . . have now found that . . . changes in brain electrical activity are induced by ketosis such that . . . mood, cognition and tolerance of pain are each affected in a positive fashion." *Id.* at 1:24–29. Further according to the Specification, "[t]he present invention relates to compounds and compositions that have the effect of modulating mammalian central nervous system activity such as to have anti-depressant effect, increase cognitive function and increase tolerance with respect to pain stimuli." *Id.* at 1:2–5.

CLAIMED SUBJECT MATTER

The claims are directed to a method of treating a subject in need of therapy for depression and/or anxiety. Claim 9 is illustrative:

> 9. A method of treating a subject in need of therapy for depression and/or anxiety, comprising orally administering to said subject 5 to 5000mg/kg body weight per day of a material selected from the group consisting of (R)-3-hydroxybutyrate, its salts, and esters of (R)-3-hydroxybutyrate with glycerol or (R)-1,3-butandiol sufficient to produce a ketosis in the subject sufficient to provide an anti-depressant effect and/or an anxiolytic effect, wherein the total

> concentration of acetoacetate and (R)-3-hydroxybutyrate in the blood is raised to between 1 and 10mM.

Appeal Br. 13 (Claims App.).

In response to the Examiner's August 26, 2015 Requirement for Restriction/Election, Appellant elected the ester of (R)-3-hydroxybutyrate with (R)-1,3-butandiol for further substantive examination. Response to Requirement for Restriction (Feb. 25, 2016); *see also* Ans. 3. We limit our consideration on the merits to the elected species. *See Ex parte Ohsaka*, 2 USPQ2d 1460, 1461 (BPAI 1987).

REJECTION

Claims 9, 10, and 15 are rejected under pre-AIA U.S.C. § 103(a) as being unpatentable over Likhodi[2] and Veech.[3]

OPINION

A. Issue

The Examiner finds that Likhodi teaches a ketogenic diet may be used to treat epilepsy because the diet is low in carbohydrates and protein, which "forces the body to utilize fat as the main source of energy in a state known as ketosis, resulting in the production of ketones, including beta-hydroxybutyrate (3-hydroxybutyrate), acetoacetate, and acetone." Ans. 3. The Examiner finds that Likhodi also teaches treating neurological disorders such as mood disorders, unipolar and bipolar depression, anxiety, and affective disorders with a ketogenic diet. *Id.* at 3–4. The Examiner finds Likhodi teaches that, because ketogentic diet has negative side effects, "it is

[2] Likhodi et al., US 2004/0097598 A1, published May 20, 2004.
[3] Veech et al., WO 2004/108740 A2, published Dec. 16, 2004.

desirable to develop . . . treatments that can mimic the effect of a ketogenic diet" for the previously mentioned neurological disorders. *Id.* at 4.

The Examiner finds that Likhodi does not explicitly teach administering the elected species, the (R)-1,3-butanediol ester of (R)-3-hydroxybutyrate. Ans. 4. However, the Examiner finds that, like Likhodi, Veech teaches that ketosis may be used to treat certain diseases such as epilepsy. *Id.* The Examiner finds Veech further teaches that administering (R)-3-hydroxybutyrate and acetoacetate or their sodium salts directly to a subject are undesirable because of, respectively, acidosis and sodium overload, and therefore teaches administering an (R)-3-hydroxybutyrate derivative, including the elected species, in a dose ranging from about 70 mg to about 5g per kg of body weight, in order to elevate blood concentrations of ketone bodies to about 0.1 to about 20 mM and ameliorate symptoms of neurological disorders. *Id.* at 4–5.

The Examiner concludes that it would have been prima facie obvious to a skilled artisan to combine Likhodi and Veech to arrive at the claimed invention, because Likhodi teaches that "neurological disorders such as epilepsy, depression, and anxiety can be treated by mimicking the effects of a ketogenic diet . . . , while Veech teaches derivatives of (R)-3-hydroxybutyrate, including [the elected species], to provide therapeutic blood concentrations of ketone bodies when administered." Ans. 5–6.

Appellant contends Likhodi teaches that it is acetone, rather than beta-hydroxybutyrate, that is "responsible for the neurological effects of the ketogenic diet." Appeal Br. 7–9. Appellant contends that Veech does not suggest that the esters of its invention can treat depression or anxiety. *Id.* at 11. Appellant further contends Veech does not suggest that such esters can

treat the same disorders as the acetone analogs taught in Likhodi and, therefore, a skilled artisan would not have been motivated to combine Likhodi and Veech. *Id.* at 10–11. Appellant contends that any combination of Likhodi and Veech would be based on impermissible hindsight. *Id.* at 11.

Appellant does not separately argue the claims. We therefore limit our analysis to claim 9 as representative. The issue with respect to this rejection is whether a preponderance of the evidence of record supports the Examiner's conclusion that claim 9 is obvious over Likhodi and Veech.

B. Findings of Fact

1. Likhodi teaches that ketogenic diet, a non-drug therapy, "forces the body to utilize fat as its major energy source," which "leads to the production of three ketones—acetoacetate, beta-hydroxybutyrate, and acetone—and a state of 'ketosis' in the body." Likhodi ¶ 11.

2. Likhodi teaches that "[t]here are several . . . reasons to believe that ketogenic diet may have utility as a mood stabilizer." *Id.* ¶ 15.

3. Likhodi teaches that disorders "for which a ketogenic diet has shown beneficial effects" or the symptoms of which "the ketogenic diet can alleviate" include "mood disorders and affective disorders (such as depression, anxiety and unipolar and bipolar illnesses)." *Id.* ¶ 65.

4. Likhodi teaches that, "[a]lthough it has few side effects, the ketogenic diet is not easy to maintain." *Id.* ¶ 17.

5. Veech teaches that the body utilizes energy obtained from the metabolism of fats during periods of carbohydrate deprivation and that, during fat metabolism, large quantities of acetoacetate and 3-hydroxybutyric acid accumulate in the blood in a condition known as ketosis. Veech 1:18–22.

6. Veech teaches that, "[m]ild ketosis, in which ketone bodies are used by the body as an energy source, has been demonstrated to have therapeutic effects in several disease states." *Id.* at 1:25–26; *see also id.* at 2:11–20).

7. Veech likewise teaches that "[t]reatment of human tissues with (*R*)-3-hydroxybutyrate results in several beneficial therapeutic and nutritional effects," including increase of cardiac efficiency and brain metabolic efficiency and reduced effects of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. *Id.* at 2:21–24, 2:29–31.

8. Veech teaches that a ketogenic diet, a high fat, low carbohydrate diet, has been suggested for inducing ketosis and achieving the beneficial effects of starvation for treating disease such as epilepsy. *Id.* at 1:28–30.

9. Veech teaches that "[t]he ketogenic diet has many drawbacks, some of which include . . . elevated triglyceride levels, cholesterol levels, or both caused by the high fact diet" as well as the fact that "the 4 to 1 ratio of fat to protein [in the ketogenic diet] is unpalatable for many subjects." *Id.* at 2:8–10.

10. Veech teaches that,

> [i]n theory, (*R*)-3-hydroxybutyrate and acetoacetate could be administered directly to achieve elevated levels of ketone bodies in a subject. However, direct administration of these compounds is impractical and dangerous. For example, direct administration of either (*R*)-3-hydroxybutyrate or acetoacetate in their acid form can result in significant acidosis following rapid absorption from the gastrointestinal tract. Administration of the sodium salt of these compounds is also unsuitable due to a potentially dangerous sodium overload that would accompany

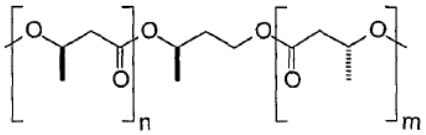
> administration of therapeutically relevant amounts of these compounds.

Id. at 3:3–10.

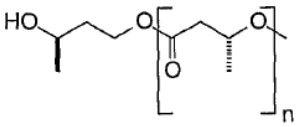
11. Veech teaches "compounds and compositions containing (*R*)-3-hydroxybutyrate derivatives effective for elevating blood concentrations of ketone bodies and methods for using such compounds and compositions as nutritional supplements or for treating medical conditions." *Id.* at 1:12–15; *see also id.* at Abstract, 4:22–5:4, 6:1–8, 6:16–19, 25:5–27:12.

12. Veech teaches that examples of its (*R*)-3-hydroxybutyrate derivatives include esters of (*R*)-3-hydroxybutyrate and oligomers of (*R*)-3-hydroxybutyrate and that "[d]isclosed ester compounds include esters derived from . . . (*R*)-1,3-butanediol," i.e., the elected species. *Id.* at 4:27–5:2.

13. Veech teaches embodiments of (*R*)-3-hydroxybutyrate derivatives according to Formulas 4 and 5, reproduced below:



Formula 4



Formula 5

Id. at 13:1–4. Veech teaches that "[p]roviding ketone bodies as (*R*)-3-hydroxybutyrate esters offers several advantages over prior known compositions," for example because "the present esters are not contaminated with significant amounts of a non-physiological stereoisomer" and thus "do

not provoke undesired side effects or suffer from competitive inhibition by the non-physiological stereoisomer." *Id.* at 13:9–13. Veech further teaches that, "[b]ecause (*R*)-3-hydroxybutyrate derivatives according to Formulas 4 and 5 release (*R*)-1,3-butanediol *in vivo,* which is oxidized to (*R*)-3-hydroxybutyrate and acetoacetate in the liver, (*R*)-1,3-butanediol is a particularly useful physiologically compatible alcohol for preparing (*R*)-3-hydroxybutyrate derivatives." *Id.* at 13:5–8.

14. Veech teaches that

> [t]he blood concentration of ketone bodies can be maintained at a therapeutically or nutritionally effective level by administering the appropriate amount of the (*R*)-3-hydroxybutyrate derivative based upon the disorder to be treated and/or the weight and energy requirements of the subject.
>
> Using the (*R*)-3-hydroxybutyrate derivatives disclosed herein, desired therapeutic and nutritional effects can be sustained without resort to the ketogenic diet. . . . Typically, therapeutic blood ketone concentrations (measured as the sum of (*R*)-3-hydroxybutyrate and acetoacetate) range from about 0.1 to about 20 mM, more typically from about 0.2 to about 10 mM, and[,] for some disorders, . . . from about 2 to about 8 mM . . . . For example, it is currently believed that ketone body concentrations greater than about 4 mM yield a therapeutic response in refractory epilepsy. . . . However, certain disorders benefit from relatively small increases in the concentration of ketone bodies in the blood. . . .
>
> . . . .
>
> . . . The amount [of (*R*)-3-hydroxybutyrate equivalents] administered can be more conveniently expressed in terms of grams . . . per day per kilogram of body weight, which typically will range from about 70 milligrams to about 5 grams per kilogram of body weight. More typically, the amount of hydroxybutyrate equivalents per day will range from about 1

> gram to about 4 grams per kilogram of body weight, and most typically from about 1.5 grams to about 3 grams per kilogram of body weight.

Id. at 27:13–28:21.

15. Veech teaches that the compounds of its invention may be administered orally. *Id.* at 6:3–8, 15:1–23, 19:4–6, 32:12–22.

C. Analysis

Likhodi and Veech both teach that a ketogenic diet, which leads to the production of certain ketone bodies (acetoacetate, beta-hydroxybutyrate (i.e., 3-hydroxybutyrate), and acetone) and a state of ketosis in the body, may be useful in treating various medical conditions. FF1–3, FF5, FF6, and FF8. Likhodi specifically teaches that disorders "for which a ketogenic diet has shown beneficial effects" or the symptoms of which "the ketogenic diet can alleviate" include "mood disorders and affective disorders (such as depression, anxiety and unipolar and bipolar illnesses)." FF3.

Both Likhodi and Veech also teach that the ketogenic diet has drawbacks, including difficulty of maintenance, lack of palatability, and elevated triglyceride and/or cholesterol levels. FF4, FF9. Veech then teaches that administration of (*R*)-3-hydroxybutyrate derivatives, including the elected species (i.e. the ester of (*R*)-3-hydroxybutyrate with (*R*)-1,3-butandiol), can achieve the desired therapeutic and nutritional effects in a subject without the need for ketogenic diet. FF11–FF14. Veech further teaches that the compounds of its invention may be administered orally. FF15.

We agree with the Examiner that, in light of the above teachings, a skilled artisan would have had a reason to treat subjects in need of therapy for depression and/or anxiety by orally administering the elected species, as

recited in claim 9, because Likhodi teaches that a ketogenic diet is effective in treating depression and anxiety and Veech teaches that orally administering the elected species can achieve the therapeutic results of a ketogenic diet.

Furthermore, Veech teaches that the compounds of its invention will typically be administered in a range of from about 70 milligrams to about 5 grams per kilogram of body weight per day. FF14. This range falls entirely within the range of 5 to 5000 mg/kg body weight per day recited in claim 9 and thus anticipates the claimed range. Similarly, Veech teaches that therapeutic blood ketone concentrations (i.e., the sum of (*R*)-3-hydroxybutyrate and acetoacetate) typically range from about 0.1 to about 20 mM. *Id.* This disclosed range overlaps with the range of total concentration of acetoacetate and (*R*)-3-hydroxybutyrate recited in claim 9, i.e., between 1 and 10mM, and renders this limitation prima facie obvious. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a prima facie case of obviousness.").

Finally, as to the limitation relating to administering an amount "sufficient to produce a ketosis in the subject sufficient to provide an anti-depressant effect and/or an anxiolytic effect," we note that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980). As Veech underscores, a skilled artisan would have been able to determine "the appropriate amount of the (*R*)-3-hydroxybutyrate derivate [to be administered] based upon the disorder to be treated." FF14. Alternatively,

we find that the Examiner has established that the prior art discloses a method that is sufficiently similar to the claimed method such that the burden is properly shifted to Appellant to show that the prior art method does not meet this limitation. *In re Best*, 562 F.2d 1252, 1254–55, (CCPA 1977) (explaining that, "'where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on'") (quoting *In re Swinehart*, 439 F.2d 210, 212–13 (CCPA 1971)).

Appellant contends that Likhodi "provides no disclosure of [(*R*)-1,3-butandiol] ester of [(R)-3-hydroxybutyrate] and certainly no suggestion of producing a total concentration of **acetoacetate and [(*R*)]-3-hydroxybutyrate in the blood** of between 1 and 10mM." Appeal Br. 9. Appellant further contends that "none of [(*R*)-3-hydroxybutyrate], salts or a glycerol or [(*R*)-1,3-butandiol ester of [(*R*)-3-hydroxybutyrate] have carbon chains of 7 to 9 carbon length." *Id.*

We are not persuaded. "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). As discussed above, in this case Veech suggests that administration of the elected species may mimic the therapeutic and nutritional effects of the ketogenic diet and further teaches a therapeutic concentration of acetoacetate

and (*R*)-3-hydroxybutyrate that overlaps the claimed concentration. FF12–FF14.

Appellant contends that Veech does not teach that the esters of its invention can treat depression or anxiety. Appeal Br. 11. Appellant also contends that a skilled artisan would not have had reason to combine Likhodi and Veech because "there is no disclosure or suggestion in Veech that such esters can treat the same disorders that long chain acetone analogs are claimed to treat in Likhodi," because "the compounds of Veech do not meet Likhodi's requirement of a carbon chain of 7 to 9 continuous carbons," and because Veech does not suggest that administration of its compounds elevate the blood levels of acetone. *Id.* at 10–11.

We are not persuaded. Once again, Appellant fails to take into account the *combination* of references. While Veech does not explicitly teach that the esters of its invention can treat depression or anxiety, it suggests that administration of such esters may mimic the therapeutic effects of the ketogenic diet, and Likhodi teaches that a ketogenic diet can alleviate symptoms of mood and affective disorders such as depression and anxiety. FF2, FF3, and FF14.

We are likewise unpersuaded by Appellant's argument that a skilled artisan would have had no reason to combine the teachings of Likhodi and Veech. As discussed above, Likhodi teaches, among other things, the therapeutic effects of a ketogenic diet, and Veech teaches that its compounds can mimic such therapeutic effects. Our reviewing court has explained that, "in a section 103 inquiry, '. . . all disclosures of the prior art . . . must be considered.'" *Merck & Co. Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278,

280 (CCPA 1976).) Thus, the fact that Likhodi and Veech focus on the effects of different compounds (acetone derivative in Likhodi and (*R*)-3-hydroxybutyrate derivatives in Veech) do not obviate the reason a skilled artisan would have had in combining the teachings of these references.

Appellant contends that Likhodi discloses that "ketones, particularly **acetone**, are responsible for the neurological effects of the ketogenic diet" and that, "whereas acetone has proven to be anticonvulsant, acetoacetate and beta-hydroxybutyrate have not." Appeal Br. 7–9, 10, 11.

We are not persuaded. Likhodi does suggest that acetone and certain of its derivatives show anticonvulsant activity and that in certain experimental models beta-hydroxybutyrate was not anticonvulsant. Likhodi Abstract, ¶¶ 21, 25, 27, and 28. However, while Likhodi teaches that its compounds may be used to treat depression and/or anxiety and "are useful in replicating therapeutic and anticonvulsant effects . . . of the ketogenic diet," *id.* ¶¶ 41–42 and 65, we do not find Likhodi teaches that all of the therapeutic effects of the ketogenic diet result from the production of acetone, or that the therapeutic effect of ketognic diet on anxiety and depression is solely the result of the production of acetone and its anticonvulsant effect during such diet.

Finally, we note that "[w]here the prior art contains 'apparently conflicting' teachings (i.e., where some references teach the combination and others teach away from it) each reference must be considered 'for its power to suggest solutions to an artisan of ordinary skill. . . . consider[ing] the degree to which one reference might accurately discredit another.'" *Medichem S.A. v. Rolabo S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re Young*, 927 F2d 588, 591 (Fed. Cir. 1991)). In this case,

Likhodi teaches there is also evidence "support[ing] a direct relationship between the level of beta-hydroxybutyrate and seizure resistance." Likhodi ¶ 22. Given this and Veech's teaching that its (*R*)-3-hydroxybutyrate may mimic the therapeutic and nutritional effects of the ketogenic diet, and given that Likhodi does not suggest that acetone is responsible for *all* of the therapeutic effects of the ketogenic diet, we agree with the Examiner that a skilled artisan would find the invention of claim 9 obvious over the combination of Likhodi and Veech.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
9, 10, 15	103(a)	Likhodi, Veech	9, 10, 15	

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). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED