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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte WEIGUANG WANG

Appeal 2018-007231
Application 13/991,608
Technology Center 1600

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and RYAN H. FLAX, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from Examiner's decision to reject claims 7, 9–12, 14, 15, and 17–21. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

[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 University of Wolverhampton (Appellant's April 4, 2018 Appeal Brief (Appeal Br.) 2).

STATEMENT OF THE CASE

Appellant's disclosure "relates to a novel disulfiram, or derivative thereof, formulation and uses thereof, in particular uses for the treatment of cancer" (Spec.[2] 1: 11–12). Appellant's claims 10, 14, 15, and 19 are representative and reproduced below:

> 10. A method of treating breast cancer in a mammal by inhibiting replication of cancer stem cells, the method comprising:
>
> providing a formulation comprising disulfiram, diethyldithiocarbamic acid, or diethyldithiocarbamate (DDC) encapsulated in a liposome, wherein the liposome increases an *in vivo* half life of the disulfiram, diethyldithiocarbamic acid, or DDC; and
>
> administering the encapsulated formulation to the mammal along with a copper containing formulation.

(Appeal Br. 22.)

> 14. A method of treating breast cancer comprising:
>
> administering to a subject a therapeutically effective amount of a disulfiram formulation comprising disulfiram, diethyldithiocarbamic acid, or diethyldithiocarbamate (DDC), encapsulated m a liposome that increases an *in vivo* half life of the disulfiram, diethyldithiocarbamic acid, or diethyldithiocarbamate (DDC).

(*Id.* at 23.)

> 15. The method of claim 14, wherein the method further comprises: simultaneously or sequentially administering a copper containing formulation, wherein the copper containing formulation is not encapsulated in the liposome.

(*Id.*)

[2] Appellant's June 4, 2013 Specification.

> 19. The method of claim 10, wherein the copper containing formulation comprises copper gluconate.

(*Id*.at 24.)

Grounds of rejection before this Panel for review:

Claims 7, 9–12, 14, 15, and 17–21 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Kennedy,[3] in combination with Ito[4] or Lobler,[5] and further in view of Leishman.[6]

Claims 19–21 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Kennedy, in combination with Ito or Lobler, and further in view of Leishman, Ferrara,[7] Slaga,[8] and Bartunek.[9]

ISSUE

Does the preponderance of evidence relied upon by Examiner support a conclusion of obviousness?

[3] Kennedy, WO 2005/009338 A2, published Feb. 3, 2005.
[4] Ito et al., *Effects of Lipid Composition on the Transcorneal Penetration of Liposomes Containing Disulfiram, a Potential Anti0cataract Agent, in the Rabbit*, 23 Biol. Pharm. Bull. 327–33 (2000).
[5] Lobler et al., *Drug delivery by nanoparticles – facing the obstacles*, 22 IFMBE Proceedings 2335–38 (2008).
[6] Leishman, US 2007/0148689 A1, published June 28, 2007.
[7] Ferrara et al., US 2013/0090591 A1, Apr. 11, 2013.
[8] Slaga et al., US 6,451,341 B1, issued Sept. 17, 2002.
[9] Bartunek et al., US 2008/0248129 A1, published Oct. 9, 2008.

FACTUAL FINDINGS (FF)

FF 1. Kennedy discloses the administration of disulfiram "in combination with metal ions provides a pharmacologic approach to inhibiting cellular proliferation of tumors" (Kennedy ¶ 15; Final Act.[10] 2–3; Ans.[11] 2–3).

FF 2. Kennedy discloses the treatment of cancers including breast cancer (Kennedy ¶ 18; *see also id.* ¶ 43; Final Act. 2–3; Ans. 2–3).

FF 3. Kennedy discloses that "[s]uitable heavy metal ions include, *inter alia*, copper" (Kennedy ¶ 15; *see also id.* ¶ 39; Final Act. 2–3; Ans. 2–3).

FF 4. Kennedy discloses, "[i]n a preferred embodiment, the heavy metal ion is administered as a complex or chelate with . . . thiuram disulfide" and "[i]n another preferred embodiment, the thiuram disulfide and the heavy metal ion are administered in combination with another anticancer agent" (Kennedy ¶ 16; Final Act. 2–3; Ans. 2–3).

FF 5. Kennedy discloses that the thiuram disulfide is preferably disulfiram (Kennedy ¶ 38; Final Act. 2–3; Ans. 2–3).

FF 6. Kennedy discloses that "[t]he thiuram disulfide compound and the heavy metal ion can be administered in combination or separately" (Kennedy ¶ 39; Final Act. 2–3; Ans. 2–3).

FF 7. Kennedy discloses the delivery of its composition "using liposomes as [a] carrier" (Kennedy ¶ 54; Final Act. 2–3; Ans. 2–3).

FF 8. Examiner finds that Kennedy "does not specifically teach the anionic part of copper salt, such as 'gluconate'" (Ans. 3; *see* Final Act. 3; *see also* Ans. 4 (Examiner finds that although Kennedy "does not teach the addition of copper as gluconate," Kennedy "teaches copper sulfate"); Final Act. 8).

[10] Examiner's August 4, 2017 Final Office Action.
[11] Examiner's May 4, 2017 Answer.

FF 9. Examiner finds that Ito and Lobler each disclose liposomal formulations comprising disulfiram (Final Act. 3 (citing Ito, Abstract and Materials and Methods; Lobler, Abstract and Materials and Methods); Ans. 3 (citing Ito, Abstract and Materials and Methods; Lobler, Abstract and Materials and Methods)).

FF 10. Leishman discloses that "[l]iposomes can . . . be used to increase the half-life of the active substance composition" (Leishman ¶ 189; *see also* Ans. 3 (citing Leishman ¶¶ 156, 189, and 200) (Examiner finds that "Leishman teaches that liposomes increase the half-life of active agents," wherein Leishman's "active agents . . . are disulfiram and DDC")).

FF 11. Examiner finds that Ferrara discloses "liposomal compositions for cancer treatment" and "the use of either copper sulfate or copper gluconate" (Ans. 4 (citing Ferrara Abstract; *id.* ¶¶ 10, 16, 157, and 233); *see also* Final Act. 8 (citing Ferrara Abstract; *id.* ¶¶ 10, 16, 157, and 233)).

FF 12. Examiner finds that Slaga discloses "compositions containing copper," "that copper has protective effect against certain cancers," and "the addition of copper as copper sulfate or copper gluconate" (Ans. 4 (citing Slaga Abstract and col. 9: 56 – 10: 2); *see* Final Act. 8 (citing Slaga Abstract and col. 9: 56 – 10: 2)).

FF 13. Examiner finds that Bartunek discloses "compositions useful for treating cancer and promoting cellular health" and "the use of copper gluconate" (Ans. 4 (citing Bartunek Abstract, Tables, Claims, and ¶¶ 86 and 90); *see* Final Act. 8 (citing Bartunek Abstract, Tables, Claims, and ¶¶ 86 and 90)).

ANALYSIS

The rejection over Kennedy, in combination with either Ito or Lobler, and further in view of Leishman:

Based on Kennedy, in combination with Ito or Lobler, and further in view of Leishman, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious

> to administer the compositions of disulfiram or diethyldithiocarbamate in liposomes for the treatment of cancer since it is art well-known that liposomes are sustained release vehicles for the delivery of anti-cancer agents and [Kennedy] is suggestive of the delivery of disulfiram or diethyldithiocarbamate along with copper for the treatment of cancer.

(Final Act. 3; *see* Ans. 3.) In this regard, Examiner reasons:

> One of ordinary skill in the art would [have] be[en] motivated to encapsulate the claimed compounds in liposomes [because] . . . Ito and Labier [each] show the knowledge in the art of encapsulating disulfiram in liposomes and Leishman teaches that liposomes increase the half-life of active agents such as disulfiram and DOC.

(Final Act. 3; *see* Ans. 3.) Examiner further reasons that although Kennedy "does not specifically teach the anionic part of copper salt, such as 'gluconate'," because it is "the cationic part of the salt which is suggested by [Kennedy] as being effective, it would have been obvious to one or ordinary skill in the art to select any salt of copper, such as copper gluconate with a reasonable expectation of success" (Final Act. 4; *see* Ans. 3).

The evidence on this record establishes that Kennedy discloses a method of treating cancer, including breast cancer, comprising the administration of disulfiram and a heavy metal ion, such as copper, in combination or separately (FF 1–6). Thus, Kennedy discloses both compounds recited in claim 10. Kennedy, Ito, and Lobler each disclose

liposomal formulations comprising disulfiram and Leishman discloses that "[l]iposomes can . . . be used to increase the half-life of [an] active substance[, such as disulfiram and DDC,] composition" (FF 7, 9, and 10), meeting the additional requirement of the claims that the disulfiram is encapsulated in a liposome. Thus, we are not persuaded by Appellant's contention that the combination of Kennedy, Leishman and either Ito or Lobler fails to suggest encapsulating an active substance, such as disulfiram or DDC, in a liposome to increase its half-life or the administration of this encapsulated disulfiram or DDC together with copper for the treatment of breast cancer (*see* Appeal Br. 16 (citing Wang Decl.[12]); *see also id.* at 18–20; Reply Br.[13] 2–4). Based on Leishman,, we find that one of ordinary skill in the art would have known that the half-life of an active agent will be increased when encapsulated in a liposome and that such a result is neither unexpected nor surprising (*see* FF 10). Therefore, we are not persuaded by Wang's statement that an increase in the half-life of an active agent encapsulated in a liposome is surprising (*see* Wang Decl. ¶ 8; *see generally id.* ¶¶ 4–7).

For the foregoing reason, we are not persuaded by Appellant's contention that Kennedy, when viewed in isolation, failed to suggest the use of a liposome to increase the half-life of an active agent (*id.* at 16–17). We are also not persuaded by Appellant's contention that Kennedy did not appreciate that its liposome will increase the half-life of its active agent, because Kennedy suggests "that to improve the half-life of an active compound, it can be *conjugated* to a water soluble non-immunogenic high

[12] Declaration of Weiguang Wang, signed October 7, 2017.
[13] Appellant's July 5, 2018 Reply Brief.

molecular weight polymer to form a polymer conjugate, which can result in a longer half-life of the active compound in the body" (*id.*). Initially, we note that Appellant's claims 10, 14, and 15 do not exclude a polymer conjugate (*see id.* at 22). Further, Leishman supports a conclusion that those of ordinary skill in this art at the time of Appellant's claimed invention knew that liposomes increase the half-life of active agents encapsulated therein (*see* FF 10). In addition, even if the prior art did not recognize that liposomes increased the half-life of an active agent, Kennedy discloses, as Appellant appreciates, liposomes comprising disulfiram (FF 7; *see also* Appeal Br. 16 (Appellant recognizes that Kennedy discloses the use of "liposomes as a carrier"); Reply Br. 2 ("Applicant does not dispute that Kennedy discloses liposomes as a delivery form for disulfiram, that Ito and Lobler disclose liposomes containing disulfiram, and that Leishman teaches that encapsulation of active agents such as disulfiram and DDC to increase their half-life")). "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Kennedy discloses the administration of disulfiram and copper "in combination or separately" (FF 6). Therefore, we are not persuaded by Appellant's contention that "Kennedy teaches that copper is preferably administered as a complex with the active ingredient . . ., rather than administered as a separate formulation, such as copper gluconate" (Appeal Br. 17; *see also id.* at 17–18). *See In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976) (A reference disclosure is not limited only to its preferred

embodiments, but is available for all that it discloses and suggests to one of ordinary skill in the art.). To be complete, we note that Appellant's claims 10, 14, and 15 are not limited to copper gluconate.

For the foregoing reasons, we are not persuaded by Appellant's contention that Examiner's rejection is based on improper hindsight (Appeal Br. 18–20; *see also* Reply Br. 2).

The rejection of claims 10, 14, and 15 under 35 U.S.C. § 103(a) as unpatentable over Kennedy, in combination with Ito or Lobler, and further in view of Leishman, is affirmed. Claims 7, 9, 11, 12, 17, 19, and 20 are not separately argued and fall with claim 10. Claims 18 and 21 is not separately argued and falls with claim 14.

The rejection over Kennedy, in combination with Ito or Lobler, and further in view of Leishman, Ferrara, Slaga, and Bartunek:

Based on Kennedy, in combination with Ito or Lobler, and further in view of Leishman, Ferrara, Slaga, and Bartunek, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious "to use copper as copper gluconate instead of sulfate taught by [Kennedy in combination with Ito or Lobler and further in view of Leishman, because] . . . Ferrara and Slaga teach the equivalency between the two salts of copper and that Bartunek teaches the addition of copper as copper gluconate" (Final Act. 8; *see also* Ans. 4; *see e.g.*, Appeal Br. 24 (Appellants' claim 19)).

Kennedy discloses the administration of disulfiram and copper "in combination or separately" (FF 6). A reference disclosure is not limited only to its preferred embodiments, but is available for all that it discloses and suggests to one of ordinary skill in the art. *See Lamberti*, 545 F.2d at

750. Therefore, we are not persuaded by Appellant's contention that because

> Kennedy teaches that copper is preferably administered as a complex with the active ingredient . . . rather than administered as a separate formulation, such as copper gluconate, . . . one of ordinary skill in the art, starting with Kennedy, would not be motivated to substitute the copper complex with a separate, copper containing formulation, e.g., copper gluconate, such that there would be no motivation, absent impermissible hindsight bias, to combine Kennedy with any of Ferrara, Slaga, or Bartunke.

(Appeal Br. 20; *see also* Reply Br. 4–5.)

"Attorney's argument in a brief cannot take the place of evidence." *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). Therefore, we are not persuaded by Appellant's unsupported assertion that

> although the remaining references teach the use of copper gluconate in the treatment of cancer among other purposes, starting with the teaching of Kennedy to mimic how copper (II) behaves in the body in the presence of disulfiram after passage through the stomach, one of ordinary skill in the art, and especially in the medical arts, would not have a reasonable expectation of success when selecting or substituting one copper salt for another, absent the present teaching.

(Reply Br. 5.)

The rejection of claim 19 under 35 U.S.C. § 103(a) as unpatentable over Kennedy, in combination with Ito or Lobler, and further in view of Leishman, Ferrara, Slaga, and Bartunek, is affirmed. Claims 20 and 21 are not separately argued and fall with claim 19.

CONCLUSION

The preponderance of evidence relied upon by Examiner supports a conclusion of obviousness.

In summary:

Claims Rejected	Basis	Affirmed	Reversed
7, 9–12, 14, 15, 17–21	§ 103 Kennedy, Ito or Lobler, Leishman	7, 9–12, 14, 15, 17–21	
19, 20, 21	§ 103 Kennedy, Ito or Lobler, Leishman, Ferrara, Slaga, Bartunek	19, 20, 21	
Overall Outcome		7, 9–12, 14, 15, 17–21	

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