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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JAN OLOF KARLSSON, TINO KURZ, and ROLF ANDERSSON

Appeal 2019-001366
Application 14/439,471
Technology Center 1600

Before ERIC B. GRIMES, DEBORAH KATZ, and MICHAEL A. VALEK, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge.*

DECISION ON APPEAL

Appellant[1] submits this appeal under 35 U.S.C. § 134(a) involving claims to methods for the treatment of selected cancers by administration of a compound of recited Formula I. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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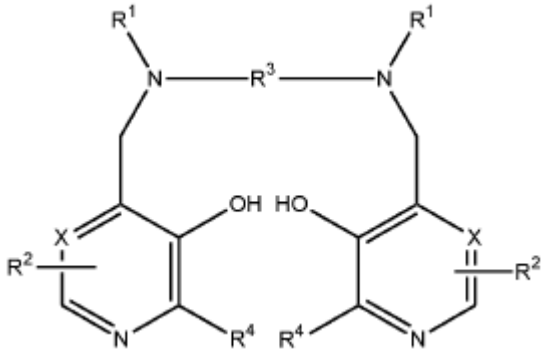
[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies PledPharma AB as the real party in interest.

STATEMENT OF THE CASE

According to the Specification, "[t]he invention . . . comprises a method employing a compound of Formula I, and in a specific embodiment, the compound DPDP [i.e., N,N'-bis-(pyridoxal-5-phosphate)-ethylenediamine-N,N'-diacetic acid] . . . for treating various cancer diseases, alone or in combination with a cyto-protective compound and/or other cytostatic drugs and/or radiotherapy." Spec. ¶ 33.

Claims 1–3, 5, 8, 20, 21, and 25 are on appeal and can be found in the Claims Appendix of the Appeal Brief. Claim 1 is illustrative and reads as follows:

> 1. A method for treatment of cancer selected from lung cancer, lung cancer metastasis, ovarian cancer, ovarian cancer metastasis, squamous cell carcinoma, squamous cell carcinoma metastasis, pancreas exocrine cancer, pancreas exocrine cancer metastasis, malignant melanoma, malignant melanoma metastasis, gastric cancer, gastric cancer metastasis, esophageal cancer, esophageal cancer metastasis, and leukemia, in a human or non-human patient in need of treatment of said cancer, said method comprising administering to said patient a cancer-inhibiting amount of a first compound of Formula I:
>
> (I)
>
> 
>
>
> or a physiologically acceptable salt thereof, wherein
>
> X is CH or N,
> each R^1 independently is hydrogen or $-CH_2COR^5$;

> R^5 is hydroxy, ethylene glycol, optionally hydroxylated alkoxy, amino or alkylamido;
> each R^2 independently is a group ZYR^6;
> Z is a bond, CO, or a C_{1-3} alkylene or oxoalkylene group, wherein said alkylene or oxoalkylene group is optionally substituted by a group R^7;
> Y is a bond, an oxygen atom or a group NR^6;
> R^6 is a hydrogen atom, $COOR^8$, an alkyl, alkenyl, cycloalkyl, aryl or aralkyl group, any of which is optionally substituted by one or more groups selected from $COOR^8$, $CONR^8_2$, NR^8_2, OR^8, $=NR^8$, =O, $OP(O)(OR^8)R^7$ and OSO_3M;
> R^7 is hydroxy, an alkyl group, or an aminoalkyl group, wherein said alkyl group or aminoalkyl group is optionally hydroxylated and/or optionally alkoxylated;
> R^8 is a hydrogen atom or an optionally hydroxylated, optionally alkoxylated alkyl group;
> M is a hydrogen atom;
> R^3 is a C_{1-8} alkylene group, a 1,2-cycloalkylene group, or a 1,2-arylene group, any of which is optionally substituted with R^7; and
> each R^4 independently is hydrogen or C_{1-3} alkyl.

Appeal Br. 40–41. Claim 5 depends from claim 1 and further recites "wherein the first compound" of Formula I is DPDP. *Id.* at 42. Claims 8 and 25 depend from claims 1 and 5 respectively and further recite "wherein the cancer is ovarian cancer and/or metastases thereof." *Id.*

Appellant seeks review of the following rejections:

I. Claims 1–3, 5, 8, 20, 21, and 25 U.S.C. § 103 as unpatentable over Armstrong[2] in view of Towart[3] and Karlsson.[4]

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[2] Deborah K. Armstrong et al., *Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer*, 354 N. Eng. J. Med., 34–43 (2006) ("Armstrong").
[3] US 6,147,094, issued Nov. 14, 2000 ("Towart").
[4] US 2010/0298271 A1, published Nov. 25, 2010 ("Karlsson").

II. Claims 1–3, 5, 8, 20, 21, and 25 for obviousness-type double patenting ("ODP") over claims 1–8 of Towart in view of Armstrong and Karlsson.

III. Claims 1–3, 5, 8, 20, 21, and 25 for ODP over claims 1–17 of Towart '828[5] in view of Towart, Armstrong, and Karlsson.

IV. Claims 1–3, 5, 8, 20, 21, and 25 for ODP over claims 1–15 of Karlsson '051[6] in view of Towart, Armstrong, and Karlsson.

V. Claims 1–3, 5, 8, 20, 21, and 25 for ODP over claims 1–7, 14, 15, 20–22, and 27–35 of Towart '895[7] in view of Towart, Armstrong, and Karlsson.

Findings of Fact

FF1. Armstrong teaches that "[i]n the United States, the standard chemotherapy for the initial treatment of ovarian cancer is a combination of a platinum analogue with paclitaxel." Armstrong 35, left col.

FF2. Towart teaches that paclitaxel is an anti-tumor agent, "which has shown anti-neoplastic action against a variety of malignant tissues, including those of the breast, colon, lung and ovary as well as in malignant melanoma," but has "a number of adverse side-effects which can include cardiovascular irregularities." Towart 1:19–27.

FF3. Towart teaches the "use of a compound of formula I . . . or a metal chelate or salt thereof in the manufacture of a therapeutic agent for use in reducing the cardiotoxicity of an anti-tumor agent, e.g.[,] an anthracycline

[5] US 6,258,828 B1, issued July 10, 2001 ("Towart '828").
[6] US 6,310,051 B1, issued Oct. 30, 2001 ("Karlsson '051").
[7] US 6,391,895 B1, issued May 21, 2002 ("Towart '895").

and/or paclitaxel." Towart 2:42–58. Towart describes DPDP as a "particularly preferred" compound of Formula I for use in this invention. *Id.* at 4:31–36.

FF4. Towart discloses data showing that both DPDP, and the manganese complex of DPDP (MnDPDP), provide a protective effect "against Doxorubicin-induced Cardiotoxicity." *See* Towart 9:40–62 (Table 2 showing that DPDP provides a 6%, 15%, and 10% protective effect at doses of 1, 10, and 30 μmole/kg respectively). According to Towart, "[e]quimolar doses of either manganese (as the chloride) or DPDP alone, although less effective [than MnDPDP] still provide a degree of protection of the atrial muscle." *Id.* at 9:14–18.

FF5. Karlsson teaches a "[c]ompound of Formula I or a salt thereof for treating cancer." Karlsson, Abstr. According to Karlsson, "[w]hen the present inventors compared MnDPDP and DPDP they surprisingly found that DPDP was more efficacious than MnDPDP in its ability to kill cancer cells and they concluded that the previously described cancer cell killing ability of MnDPDP is an inherent property of DPDP." *Id.* ¶¶ 54, 73, 77.

Analysis

I. 103 Rejection: Armstrong, Towart, and Karlsson

The issue for this rejection is: Does the preponderance of evidence of record support Examiner's conclusion that the method in claims 1–3, 5, 8, 20, 21, and 25 is obvious over the cited references?

Claim 1

Examiner determines that

> [a] person of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in administering [DPDP] to a human ovarian cancer patient

> receiving intraperitoneal paclitaxel and cisplatin chemotherapy for ovarian cancer to prevent or treat the well-known cardiotoxic effects of paclitaxel therapy. The skilled artisan would have been motivated to do so in view of the fact that (i) Armstrong et al. clearly teaches the efficacy of paclitaxel and cisplatin therapy for ovarian cancer, with associated grade 3 and 4 cardiovascular toxicity; (ii) Towart et al. clearly teaches the cardiotoxic effects of paclitaxel administration; and (iii) Towart et al. teaches the dipyridoxal agent [DPDP] as a known cardioprotective agent effective to treat or minimize cardiotoxicity associated with paclitaxel administration. It would, therefore, have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to administer [DPDP] to a human ovarian cancer patient receiving intraperitoneal cisplatin and paclitaxel chemotherapy to minimize paclitaxel cardiotoxicity.

Ans. 5. Examiner concludes that administering DPDP at the doses taught in Towart would inherently provide "a cancer-inhibiting amount," as recited in claim 1, because Karlsson teaches "that cancer cell-killing properties of DPDP are inherent to the compound." *Id.*

Appellant argues that Towart "does not provide any teaching of a compound of Formula I having cancer inhibiting activity, and . . . does not provide any teaching of administering a compound of Formula I to a patient in need of treatment of a cancer selected from the group recited in claim 1 in a cancer-inhibiting amount." Appeal Br. 9. According to Appellant, those skilled in the art as of the priority date of the present application "recognized that the cardioprotective uses of the compounds disclosed in Towart '094 are derived from their superoxide dismutase (SOD) mimetic activity, which is attributable to the metal component of the metal chelates, specifically manganese." *Id.* Thus, urges Appellant, one skilled in the art, following "the then-accepted wisdom, would have used a manganese chelate

compound," such as MnDPDP, not a "non-manganese compound[] of Formula I," like DPDP, to provide a cardioprotective effect. *Id.* at 10. In addition, Appellant contends that because Karlsson was rejected as "not enabling under 35 U.S.C. 112, first paragraph, for treating every known cancer" during prosecution, it "cannot be relied [on] in a rejection under 35 U.S.C. 103 as teaching . . . that a compound of Formula I is inherently effective for treating every known cancer or, specifically, treating the cancers recited in claim 1." *Id.* at 11.

Based on the record before us, we determine that the preponderance of the evidence supports Examiner's rejection of claim 1 over the cited references. We agree with, and adopt, Examiner's findings (*see* FF1–FF5) and reasoning in support of that rejection. We are not persuaded by Appellant's arguments, which we address below.

Appellant's argument that a skilled artisan would not have considered administration of DPDP to provide a cardioprotective effect for an ovarian cancer patient being treated with paclitaxel is not persuasive. Towart specifically teaches that DPDP provides a protective effect against cardiotoxic side effects of such drugs. FF4. Accordingly, Towart supports Examiner's finding that a skilled artisan would be motivated to administer DPDP with paclitaxel to treat ovarian cancer and would have a reasonable expectation the DPDP would provide a protective effect against cardiotoxic side effects. Ans. 5. The evidence Appellant cites in the Appeal Brief attributes the protective effect provided by "MnDPDP and its dephosphorylated counterpart MnPLED" to their "superoxide dismutase (SOD) mimetic activity." *See* Appeal Br. 9–10 (quoting US 8,377,969 B2, 1:44–61). But that evidence says nothing about the protective effect that

Towart teaches the use of DPDP "alone" provides, nor does it address the data in Towart demonstrating that administration of DPDP, in fact, provides such an effect. FF4. Moreover, contrary to Appellant's assertion (*see* Appeal Br. 11–12), the evidence it cites concerning SOD mimetic activity does not teach away from the use of DPDP to provide a cardioprotective effect because it does not "criticize, discredit, or otherwise discourage investigation into" the use of DPDP for that purpose. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009)).

We are also unpersuaded by Appellant's argument that the teachings in Karlsson cannot be considered because that reference does not enable treatment of "every known cancer." *See* Appeal Br. 11. It is well-settled that "a non-enabling reference may qualify as prior art for the purpose of determining obviousness under § 103." *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991); *see also Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) ("[e]ven if a reference discloses an inoperative device, it is prior art for all that it teaches"). Here, Karlsson teaches that the "cancer cell killing ability of MnDPDP is an inherent property of DPDP." FF5. Thus, Karlsson supports Examiner's determination that the administration of DPDP, in the amounts taught in Towart,[8] would inherently be cancer-inhibiting and, therefore, that

[8] Towart teaches that DPDP exhibited a protective effect at 1, 10, and 30 μmole/kg. FF4. These amounts overlap with the dosage range described in Appellant's Specification. Spec. ¶ 47; *see also 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

claim 1 would have been obvious over the cited combination of references. For these reasons, we affirm the rejection.

Claims 2, 3, and 5

Claims 2, 3, and 5 further "define the compound of Formula I" administered according to claim 1. *See* Appeal Br. 12–13. But the compound DPDP remains within the scope of each of these claims. *See* Appeal Br. 12–13. Thus, claims 2, 3, and 5 read upon the combination of Armstrong, Towart, and Karlsson, as articulated by Examiner for claim 1. Appellant does not present any additional reason why Examiner's rejection should be reversed for these claims. Accordingly, we determine the preponderance of the evidence supports the rejection of claims 2, 3, and 5 for the same reasons articulated above.

Claims 8 and 25

Claims 8 and 25 additionally "recite that the cancer is ovarian cancer and/or metastases thereof." *See* Appeal Br. 13–14. Thus, each of these claims reads upon the combination of Armstrong, Towart, and Karlsson, as articulated by Examiner for claim 1. Appellant does not present any additional reason why Examiner's rejection should be reversed for these claims. Accordingly, we determine the preponderance of the evidence supports the rejection of claims 8 and 25 for the same reasons articulated above.

Claims 20 and 21

Claims 20 and 21 additionally "recite that the first compound, i.e., the compound of Formula I, is administered together with one or more other

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range establishes a *prima facie case* of obviousness.").

anti-cancer drugs selected from" a group that includes paclitaxel. *See* Appeal Br. 14–15. Thus, each of these claims reads upon the combination of Armstrong, Towart, and Karlsson, as articulated by Examiner for claim 1.

Appellant argues claims 20 and 21 are further patentable over that combination because Armstrong does not teach paclitaxel in combination with a compound of Formula I and Towart does not teach a compound of Formula I in combination with paclitaxel in a cancer-inhibiting amount. *See* Appeal Br. 15. That argument is unpersuasive for several reasons. First, as our reviewing Court has explained, "non-obviousness cannot be established by attacking references individually where the rejection is based on the teachings of a combination of references." *Soft Gel Techs., Inc. v. Jarrow Formulas, Inc.*, 864 F.3d 1334, 1341 (Fed. Cir. 2017) (quoting *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986)). Second, Towart does, in fact, teach the administration of a compound of Formula I, e.g., DPDP, in combination with paclitaxel to provide a protective effect against cardiotoxic side effects. FF2, FF3. And, as explained above in our analysis of claim 1, the record supports that the amounts of DPDP taught to have a protective effect in Towart (*see* FF4) are inherently cancer-inhibiting. For these reasons, Examiner's obviousness rejection of claims 20 and 21 is supported by the preponderance of the evidence.

II. ODP Rejection: Towart Claims 1–8, Armstrong, and Karlsson

The issue for this rejection is: Does the preponderance of evidence of record support Examiner's conclusion that the method in claims 1–3, 5, 8, 20, 21, and 25 is obvious over claims 1–8 of Towart in view of Armstrong and Karlsson?

Since it involves the same references as the obviousness rejection, Examiner premises this ODP rejection on findings similar to those described above. *See* Ans. 7–9. Appellant contends that the present claims are patentably distinct from claims 1–8 of Towart because "[a] method for treating a cancer selected from the group recited in claim 1 is not an obvious variation of a method of reducing the cardiotoxicity of an anti-tumor agent." Appeal Br. 16.

We are not persuaded by Appellant's argument. In particular, claim 4 of Towart recites the simultaneous administration of a compound of Formula I, such as DPDP, and paclitaxel. Towart 12:19–20. While the claims of Towart do not recite that DPDP has cancer-inhibiting activity, the record supports that such activity is in inherent property of DPDP. FF5. Thus, the administration of DPDP as claimed in Towart would inherently provide the cancer-inhibiting activity recited in Appellant's claims. That Towart's claims recite that the administration of Formula I for a different, albeit related, purpose, i.e., to provide a protective effect against cardiotoxic side effects of a chemotherapeutic agent like paclitaxel as opposed to acting as a chemotherapeutic agent itself, does not distinguish Appellant's claims. The record supports that paclitaxel was a known drug for treating ovarian cancer. FF1, FF2. Thus, it would have been obvious to use the method of Towart claim 4 to treat a patient with ovarian cancer as recited in Appellant's claims.

In addition to the argument above, Appellant repeats the same arguments it presented for the obviousness rejection of claim 1 and for its groupings of claims 2, 3, and 5; claims 8 and 25; and claims 20 and 21. *See* Appeal Br. at 17–21. We are not persuaded by those arguments for the same

reasons articulated above. Accordingly, we determine that Examiner's rejection of claims 1–3, 5, 8, 20, 21, and 25 for ODP over claims 1–8 of Towart in view of Armstrong and Karlsson is supported by the preponderance of the evidence.

III. Examiner's Other ODP Rejections

Examiner groups the other three ODP rejections together, basing them on a common finding that the specified claims of Towart '828, Karlsson '051, and Towart '895 "provide[] for a product of [DPDP] and/or methods of administering [DPDP] to a subject for therapeutic purposes." Ans. 10. Thus, according to Examiner, these claims are directed to obvious variations of the methods recited in Appellant's claims. *Id.* at 10–11. We determine these rejections are not supported by the preponderance of the evidence.

The claims of these references are not directed to treating cancer, nor has Examiner shown that they are directed to related treatments such as reducing side effects associated with cancer therapy. Unlike the claims of Towart, the claims of these references do not recite the co-administration of a compound of Formula I with paclitaxel or another drug known for treating the types of cancer recited in Appellant's claims. Indeed, the claims these ODP rejections are based upon appear to be drawn to wholly unrelated indications. *See, e.g.*, Karlsson '051 claim 1 (reciting a "method of treatment . . . to combat or prevent atherosclerosis"). Examiner has not sufficiently articulated why one of ordinary skill in the art would consider such claims to be obvious variations of the methods in claims 1–3, 5, 8, 20, 21, and 25 of Appellant's present application. Accordingly, we reverse Examiner's other ODP rejections.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–3, 5, 8, 20, 21, 25	103	Armstrong, Towart, Karlsson	1–3, 5, 8, 20, 21, 25	
1–3, 5, 8, 20, 21, 25		Nonstatutory Double Patenting: Towart	1–3, 5, 8, 20, 21, 25	
1–3, 5, 8, 20, 21, 25		Nonstatutory Double Patenting: Towart ’828		1–3, 5, 8, 20, 21, 25
1–3, 5, 8, 20, 21, 25		Nonstatutory Double Patenting: Karlsson ’051		1–3, 5, 8, 20, 21, 25
1–3, 5, 8, 20, 21, 25		Nonstatutory Double Patenting: Towart ’895		1–3, 5, 8, 20, 21, 25
Overall Outcome			1–3, 5, 8, 20, 21, 25	

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED