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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CHIH-PENG LIU, YA-CHIN LO, MING-CHENG WEI, MAGGIE LU, SHUEN-HSIANG CHOU, SHIH-TA CHEN, and HSIANG-WEN TSENG[1]

Appeal 2018-002755
Application 15/142,170
Technology Center 1600

Before ERIC B. GRIMES, JEFFREY N. FREDMAN, and RYAN H. FLAX, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method of treating cancer, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM-IN-PART, but designate the affirmance a new ground of rejection.

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[1] Appellant identifies the real party in interest as INDUSTRIAL TECHNOLOGY RESEARCH INSTITUTE. Appeal Br. 1. We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a).

STATEMENT OF THE CASE

"Hyaluronic acid (HA) is a natural polysaccharide . . . that is distributed into the lymphatic system and is a ligand for the CD44 receptor, which is overexpressed in lymphatic tumors." Spec. ¶ 6. The Specification discloses "a method of treating lymphatic cancer using hyaluronan nanoparticles. The hyaluronan nanoparticles may comprise a hyaluronic acid derivative and a platinum compound. The hyaluronic acid derivative itself may comprise: a hyaluronic acid; a modified histidine [and] optionally a polymer or C_4-C_{20} alkyl." *Id.* ¶ 7.

Claims 1–25 are on appeal. Claim 1, reproduced below, is illustrative:

> 1. A method of treating a tumor in a lymphatic system of a subject, comprising:
>
> administering a hyaluronan nanoparticle comprising a hyaluronic acid derivative and a platinum compound to the subject with tumors in the lymphatic system, wherein the hyaluronic acid derivative comprises:
>
> hyaluronic acid,
>
> modified histidine, and
>
> optionally at least one of a polymer or a C_4–C_{20} alkyl,
>
> wherein the modified histidine and the optional at least one of polymer or C_4–C_{20} alkyl are grafted at least to primary hydroxyl groups of the hyaluronic acid, and
>
> wherein a graft ratio of the modified histidine is within 20–100%, and a graft ratio of the optional at least one of polymer or C_4–C_{20} alkyl is within 0–40% based upon the total number of hydroxyl groups on the hyaluronic acid.

OPINION

Obviousness

Claims 1–25 stand rejected under 35 U.S.C. § 103 as obvious based on Forrest,[2] Wu,[3] Shih,[4] and either Pitarresi[5] or Lo.[6] Ans. 4. The Examiner finds that "**Forrest et al** teach methods of administering the chemotherapeutic agents using HA based nano-carriers to target tumors in the lymphatic system." *Id.* at 7. The Examiner also finds that

> **Wu et al** or **Shih et al** teach histidine-hyaluronic acid conjugate nanoparticles as carriers, **Pitarresi et al** teach synthesis of novel graft copolymers of hyaluronan, polyethyleneglycol and polylactic acid, and **Lo et al** teach hyaluronic acid grafted with a modified histidine and a polymer or C_4–C_{20} alkane. This suggests technology of grafting side chains on HA, can be charged or neutral, is well known in the art.

Id.

The Examiner concludes that the claimed method would have been obvious to those skilled in the art because "one is motivated to use known structurally similar HA based nano-carriers in targeting lymphatic system in a subject." *Id.*

We agree with the Examiner's conclusion but, in our view, the rejection is not based on the most pertinent disclosures in the cited

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[2] Forrest et al., US 2012/0100218 A1, published Apr. 26, 2012.
[3] Wu et al., et al., Preparation and characterization of nanoparticles based on histidine-hyaluronic acid conjugates as doxorubicin carriers, *Journal of Materials Science: Materials in Medicine*, 23(8):1921–29 (2012).
[4] Shih et al., US 2014/0186415 A1, published July 3, 2014.
[5] Pitarresi et al., Synthesis of novel graft copolymers of hyaluronan, polyethyleneglycol and polylactic acid, *MMAIJ*, 3(2):53–56 (2007).
[6] Lo et al., US 2015/0118322 A1, published Apr. 30, 2015.

references. Specifically, Lo discloses a composition that meets all of the structural limitations of claim 1, and therefore constitutes the closest prior art for purposes of analyzing obviousness.

Lo discloses

> a biomedical composition, comprising: a hyaluronic acid; a modified histidine; and a polymer or C_4–C_{20} alkane, wherein the modified histidine and the polymer or C_4–C_{20} alkane are grafted to at least one primary hydroxyl group of the hyaluronic acid to allow the hyaluronic acid to form a hyaluronic acid derivative, wherein a graft ratio of the modified histidine is about 1–100%, and a graft ratio of the polymer or C_4–C_{20} alkane is about 0–40%.

Lo ¶ 8. Thus, Lo discloses a hyaluronic acid derivative comprising hyaluronic acid (HA), modified histidine (His), a polymer or C_4–C_{20} alkyl group, with the modified His and polymer/alkyl group grafted to at least one primary hydroxyl group of HA, with graft ratios that are the same as or encompass those recited in claim 1.

Lo discloses that "the biomedical composition . . . may further comprise an active ingredient with a positive charge in water." *Id*. ¶ 43. "The . . . active ingredient with a positive charge in water may comprise a drug (such as antibiotics, platinum-based antineoplastic drugs)." *Id.* ¶ 45. Thus, Lo expressly suggests including a platinum compound in its composition.

Lo states that

> the active ingredient with a positive charge in water and a carboxyl group of the hyaluronic acid derivative repulse each other due to different charge, and furthermore, by a hydrophobic effect produced from the modified histidine grafted on the hyaluronic acid and used to modify the hyaluronic acid, the active ingredient can be agglomerated, and make the active ingredient with a positive charge in water

> mentioned above be packaged in the preceding hyaluronic acid derivative.

Id. ¶ 43. Thus, Lo states that the HA derivative and platinum compound agglomerate, and therefore Lo's composition reasonably appears to meet the limitation of a "hyaluronan nanoparticle," as recited in claim 1.

Based on the above disclosures, Lo would have made obvious a composition meeting all of the structural limitations recited in claim 1. In view of Lo's suggestion to include "platinum-based *antineoplastic* drugs" (*id*. ¶ 45, emphasis added), such as cisplatin (*id.* ¶ 47), a skilled artisan would have considered it obvious to administer the composition to a patient having a tumor, because antineoplastic drugs such as cisplatin are used to treat cancer.

Lo teaches that its composition can be administered in several ways, including parenterally; e.g., subcutaneously or intracutaneously. *Id*. ¶ 53. Lo also teaches that its composition addresses the need in the art for a "drug delivery system that has high bio-compatibility, and that can be designed to release a drug only in an appropriate environment." *Id.* ¶ 7. More specifically, "as compared with a level of pH 7.4, hyaluronic acid derivative/doxorubicin complex nano-carriers . . . have higher cumulative drug release rates at pH 5.0 (greater than 2.5 fold)." *Id.* ¶ 133.

Lo thus makes obvious all of the limitations of claim 1 except that it does not suggest treating a subject with a tumor specifically in the lymphatic system. Forrest, however, discloses a composition comprising "a nanoconjugate comprising: a nanocarrier configured for preferential intralymphatic accumulation after percutaneous or interstitial administration;

and a plurality of chemotherapeutic agents coupled to the nanocarrier." Forrest ¶ 11.

Forrest discloses that its composition "includes a nanocarrier that is optimized in size and composition to preferentially be translocated into the lymphatic system rather than spread and concentrate systemically. It has been found that hyaluronan polymeric carriers and some dendritic carriers, such as those described herein, have such a[] selective translocation characteristic into the lymphatic system." *Id*. ¶ 55.

"The chemotherapeutic agents are preferably selected from the group consisting of cisplatin, doxorubicin, and docetaxel." *Id*. ¶ 12. "Cisplatin is one of the most widely used chemotherapy agents for solid tumors; however, its toxicity and resistance severely limits its dose and use in many patients." *Id.* ¶ 56. Forrest states that its "invention can include a nanoconjugate of the polysaccharide hyaluronan ('HA') with a chemotherapeutic drug (e.g., cisplatin or other platinum)." *Id.* ¶ 60. "The HA nanoconjugate is formulated with a molecular weight/size of HA that is effective in concentrating cisplatin to the breast lymphatics, and reduce peak plasma concentrations that are toxic." *Id.*

Based on Forrest's disclosure, it would have been obvious to a person of ordinary skill in the art to administer Lo's composition to a patient having a tumor in their lymphatic system, because Lo's composition comprises nanoconjugates of a platinum-based antineoplastic compound (e.g., cisplatin) and a hyaluronic acid derivative, and Forrest teaches that nanoconjugates of hyaluronic acid with a chemotherapeutic drug (e.g., cisplatin) are preferentially translocated to the lymphatic system.

Forrest teaches that the cisplatin is concentrated to the breast lymphatics by the HA conjugate, thus reducing toxicity. A skilled artisan therefore would have expected that administering Lo's composition to a patient with a tumor in the lymphatic system would result in reduced cisplatin toxicity.

The teachings of Wu, Shih, and Pitarresi are not necessary for a prima facie case of obviousness with respect to claim 1.

Appellant argues that "one of ordinary skill in the art would not have a reasonable expectation of success in intralymphatic delivery of a platinum compound to treat a tumor in a lymphatic system of a subject based on such a combination." Appeal Br. 6. Appellant argues that Forrest's disclosure shows that "that knowledge of intralymphatic delivery of hyaluronic acid by subcutaneous administration as of the filing of Forrest is limited to the experiments conducted in Forrest." *Id.* at 7. Appellant also argues that the "relationship between chemical structures and pharmacology has long been known to be an unpredictable art." *Id.* at 8.

These arguments are unpersuasive. Forrest discloses that its nanoconjugates of HA and a chemotherapeutic drug accumulate in cancerous cells in the lymphatic system. Forrest ¶¶ 59–60. Forrest discloses that the molecular weight of the HA affects the lymphatic drug concentration, and states that the optimal molecular weight is between 10 kD and 200 kD. *Id.* ¶¶ 67–68. Forrest also discloses that the size of the nanoconjugates affects their translocation to the lymphatic system, and states that sizes between about 10 nm and 80 nm are appropriate. *Id.* ¶ 70. Thus, Forrest provides a reasonable amount of guidance regarding which

parameters are important for intralymphatic delivery, and what values of those parameters are suitable. Appellant has not pointed to persuasive evidence showing that undue experimentation would have been required to modify Lo's composition in such a way as to achieve the lymphatic accumulation disclosed by Forrest.

Appellant argues that Wu, Shih, and Pitarresi do not cure the alleged deficiencies of Forrest. Appeal Br. 10–11. Similarly, Appellant argues that Wu, Shih, Lo, and Pitarresi disclose different structural modifications of hyaluronic acid, and therefore conflict with each other. *Id.* at 11.

These arguments are unpersuasive because, as discussed above, Lo and Forrest support a prima facie case of obviousness. Wu, Shih, and Pitarresi are cumulative and unnecessary to the prima facie case.

With regard to Lo, Appellant argues

> Lo discloses a modified hyaluronic acid for controlled drug release. This function in Lo has no disclosed effect in the prior art on intralymphatic delivery. . . . There is no motivation for one of ordinary skill in the art to use the hyaluronic acid modifications in Lo to the hyaluronan nanoparticle in Forrest, because there is no reasonable expectation of success that intralymphatic delivery can occur with the modifications in Lo.

Id.

This argument is also unpersuasive. Even though Lo does not disclose that its compounds accumulate in the lymphatic system, it discloses that the hyaluronic acid derivative and active agent in its composition agglomerate. Lo ¶ 43. Thus, a skilled artisan would recognize that they are structurally similar to Forrest's "nanoconjugate[s] of the polysaccharide hyaluronan ('HA') with a chemotherapeutic drug (e.g., cisplatin or other platinum)." Forrest ¶ 60. And, as previously discussed, Appellant has not shown that any

modifications of Lo's agglomerates necessary for intralymphatic delivery would have required undue experimentation.

Appellant lists each of the dependent claims under its own subheading. Appeal Br. 11–17. However, with regard to claims 2–5, 12–15, 17, and 19, Appellant's only argument is that "there is no motivation to combine the primary reference of Forrest with the secondary references as presented under claim 1." *Id.* at 11. That argument is unpersuasive for the reasons discussed above.

Appellant separately argues claims 6–11. Appeal Br. 12–14. Appellant acknowledges that Lo discloses the Boc-histidine and graft ratio recited in dependent claims 6 and 7, as well as the polyethylene glycol and graft ratio recited in dependent claims 8 and 9, and the combined Boc-histidine and polyethylene glycol modifications recited in dependent claims 10 and 11. *Id.* Appellant argues, however, that "Wu teaches different modifications of hyaluronic acid by histidine than Lo, and Pitarresi teaches different modifications of hyaluronic acid by polyethylene glycol than Lo." *Id.* at 14.

Similarly, Appellant acknowledges that "Lo discloses polyethylene glycol and DACHPt," as recited in claim 16, and "Lo discloses linking groups for a polymer (Formula (IV))," as recited in claim 18. *Id*. at 15. Appellant argues, however, that "Pitarresi discloses a different substitution of hyaluronic acid polymer than Lo." *Id.*

The arguments presented with respect to claims 6–11, 16, and 18 are unpersuasive because the disclosures of Wu and Pitarresi are not required to show that these claims would have been obvious to a skilled artisan—as

Appellant concedes, Lo by itself discloses the limitations added to claim 1 by each of claims 6–11, 16, and 18. The additional limitations therefore would have been obvious to a skilled artisan based on Lo and Forrest.

Claims 20–23 add limitations regarding the route of administration: claims 20–22 recite parenteral, including subcutaneous, administration; and claim 23 is limited to intravenous injection. With respect to claims 20–22, Appellant argues that the types of administration, including "subcutaneous administration[,] in Lo is not applied to intralymphatic delivery. There is no reasonable expectation of success in applying the subcutaneous administration in Forrest to a hyaluronan nanoparticle modified according to the secondary references." Appeal Br. 16.

This argument is not persuasive. Lo discloses that its composition can be administered parenterally, including subcutaneous or intracutaneous administration. Lo ¶ 53. Forrest states that its "nanoconjugates can be subcutaneously administered for accumulation in intralymphatic tissue." Forrest ¶ 59. Forrest's nanoconjugates, like those of Lo, "include a nanoconjugate of the polysaccharide hyaluronan ('HA') with a chemotherapeutic drug (e.g., cisplatin or other platinum." *Id.* ¶ 60. Although Lo's nanoconjugates also include a modified histidine and a polymer grafted to the HA moiety, Appellant has not provided evidence or sound technical reasoning to show that those differences would have led a skilled artisan to expect Lo's HA/cisplatin nanoconjugates to behave differently from Forrest's HA/cisplatin nanoconjugates.

With regard to claim 23, Appellant argues that "Lo discloses intravenous administration ([0053]). However, the intravenous

administration in Lo is not applied to intralymphatic delivery." Appeal Br. 17.

We agree with Appellant that the cited references would not have provided a reasonable expectation of success in administering the nanoconjugates disclosed by Lo intravenously to treat a patient having a tumor in the lymphatic system. Lo discloses that its nanoconjugates can be administered intravenously. Lo ¶ 53. However, Lo does not expressly suggest treating tumors in the lymphatic system. Forrest does teach administering its compounds to treat lymphatic system tumors. Forrest ¶ 53. However, Forrest expressly states that its composition "is not systemically administered. That is, the formulation is not administered via intravenous administration." *Id.* Thus, the combined teachings of Lo and Forrest would not have provided a skilled artisan with a reasonable expectation of success in treating a lymphatic system tumor by administering Lo's composition intravenously. The Examiner has not pointed to any disclosure in Wu, Shih, or Pitarresi that makes up for this deficiency in Lo and Forrest. We therefore reverse the rejection of claim 23.

With regard to claims 24 and 25, Appellant argues that "Forrest discloses metastatic tumors. However, there is no motivation or reasonable expectation of success in using the hyaluronan nanoparticle of Forrest modified by the secondary references." Appeal Br. 17.

This argument is unpersuasive. Forrest states that "[t]he subcutaneous administration of a nanoconjugate that can accumulate in intralymphatic tissues is beneficial for treating many cancers, such as breast cancers," as recited in claim 25. *See* Forrest ¶ 59. Forrest also states that its

"nanoconjugates . . . accumulate in the cancerous cells that are present in the lymphatic system and/or intralymphatic tissues and thereby act on lymphatic *metastases* without undesirable systemic toxicities." *Id.* (emphasis added). Appellant has not provided evidence or sound technical reasoning to show that a skilled artisan would not have expected Lo's similar nanoconjugates to also accumulate in the lymphatic system, and thus also be effective in treating metastatic tumors, including breast cancer.

CONCLUSION

We affirm the rejection of claims 1–22, 24, and 25 under 35 U.S.C. § 103 based on Forrest, Wu, Shih, and either Pitarresi or Lo. Because our fact-finding and reasoning differ substantially from that of the Examiner, however, we designate the affirmance a new ground of rejection in order to give Appellant a fair opportunity to respond. *See In re Kronig*, 539 F.2d 1300, 1302–03 (CCPA 1976).

We reverse the rejection of claim 23 under 35 U.S.C. § 103 based on Forrest, Wu, Shih, and either Pitarresi or Lo.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/ Basis	Affirmed	Reversed	New Ground
1–25	103	Forrest, Wu, Shih, Pitarresi, Lo	1–22, 24, 25	23	1–22, 24, 25

TIME PERIOD FOR RESPONSE

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

> When the Board enters such a non-final decision, the appellant, 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 prosecution will be remanded to the examiner. The new ground of rejection is binding upon the examiner unless an amendment or new Evidence not previously of Record is made which, in the opinion of the examiner, overcomes the new ground of rejection designated in the decision. Should the examiner reject the claims, appellant may again appeal to the Board pursuant to this subpart.
>
> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same Record. The request for rehearing must address any new ground of rejection and state with particularity the points believed to have been misapprehended or overlooked in entering the new ground of rejection and also state all other grounds upon which rehearing is sought.

Further guidance on responding to a new ground of rejection can be found in the Manual of Patent Examining Procedure § 1214.01.

AFFIRMED IN PART; 37 C.F.R. § 41.50(b)