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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DANIEL A. HELLER and YOSEF SHAMAY[1]

Appeal 2017-006528
Application 14/689,683
Technology Center 1600

Before ULRIKE W. JENKS, KRISTI L. R. SAWERT, and DAVID COTTA, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge.*

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant appeals from Examiner's decision to reject claims directed to a polymeric nanogel with affinity to P-selectin as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] Appellant is the Applicant, Memorial Sloan Kettering Cancer Center, which according to the brief is the real party in interest. Appeal Br. 2.

STATEMENT OF THE CASE

According to the Specification,

> [f]ucoidans are a class of sulfated, fucose-rich polymers that can be found, for example, in brown macroalgae. Fucoidans have been reported to have anticoagulant, antiviral, anti-inflammatory, and anticancer activities, as well as high affinity to P-selectin. P-selectin is an inflammatory cell adhesion molecule responsible for leukocyte recruitment and platelet binding.

Spec. ¶ 5. The Specification states that "P-selectin is the new target for drug delivery in various cancers." *Id.* ¶ 12. "Nanogels -- porous nanoscale hydrogel networks -- are a class of nanomaterials with tunable chemical properties that facilitate targeting and delivery to specific tissues. They are intrinsically porous and can be loaded with small drugs or macromolecules by physical entrapment, covalent conjugation or controlled self-assembly." *Id.* ¶ 4.

Claims 1–5, 7–15, and 30–32 are on appeal, and can be found in the Claims Appendix of the Appeal Brief. Claim 1 is representative of the claims on appeal, and reads as follows:

> 1. A polymeric nanogel with affinity to P-selectin, the nanogel comprising:
>
> (i) a sulfated polymer species comprising free hydroxyl moieties and sulfate moieties capable of targeting P-selectin;
>
> (ii) a drug; and
>
> (iii) polyethylene glycol (PEG), wherein the drug is conjugated to the polyethylene glycol via hydrozone linkages.

Appeal Br. 19 (Claims Appendix).

Appellant requests review of the following grounds of rejection made by Examiner:

I. Claims 1–5, 7–13, and 30–32 under 35 U.S.C. § 103(a) as unpatentable over Sezer[2] in view of Huan.[3]

II. Claims 1–5, 7–13, 15, and 30–32 under 35 U.S.C. § 103(a) as unpatentable over Sezer in view of Huan in further view Chung.[4]

III. Claims 1–5, 7–14, and 30–32 under 35 U.S.C. § 103(a) as unpatentable over Sezer in view of Huan in further view Zhang.[5]

Obviousness over Sezer and Huan

Examiner's position is that Sezer and Huan in combination disclose nanogel particles comprising fucoidan and a drug. Ans. 2. "The particles [of Sezer] are made of chitosan-fucoidan (a hydrogel)." *Id.* Sezer further discloses that fucoidan can be found on the surface of the particle. *Id.* Examiner acknowledges that Sezer fails to teach a drug that is conjugated to PEG (e.g., "a DOX-PEG-DOX construct"). *Id.* Examiner looks to Huan for teaching this drug. *Id.*

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[2] Ali Demir Sezer, WO 2006/091180 A2, published Aug. 31, 2006 ("Sezer").

[3] Menglei Huan et al., *In Vitro and In Vivo Antitumor Activity of a Novel pH Activated Polymeric Drug Delivery System for Doxorubicin*, 7 PLOS ONE 1–11 (2012) ("Huan").

[4] Leland W.K. Chung et al., US 2011/0085974 A1, published Apr. 14, 2011 ("Chung").

[5] Zhongyuan Zhang et al., *Fucoidan Extract Enhances the Anti-Cancer Activity of Chemotherapeutic Agents in MDA-MB-231 and MCF-7 Breast Cancer Cells*, 11 MAR. DRUGS 81–98 (2013) ("Zhang").

Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute one active agent for another. Specifically, it would have been obvious to incorporate DOX-PEG-DOX into the particles of Sezer because the DOX-PEG-DOX compound was demonstrated to have higher cytotoxicity against cancer than doxorubicin alone. Ans. 3. The Examiner states: "The rationale for this is that Sezer teaches methods of treatment of diseases using its formulation. By incorporating DOX-PEG-DOX into the formulation of Sezer, the formulation of Sezer may be used to treat cancer." Final Act. 3.[6]

The issue is: Does the evidence of record support Examiner's conclusion that the combination of Sezer and Huan teach a nanogel comprising a sulfated polymer, a drug, and PEG as claimed?

Findings of Fact

FF1. Sezer teaches using fucoidan multiparticulate systems as a drug carrier. Sezer 3:7. "[F]ucoidan, a polysaccharide; which is obtained from algae and due to the sulfates in its structure shows an anionic character." *Id.* at 3:15–17. To form the multiparticulate structure, fucoidan is mixed with chitosan, another polysaccharide with cationic properties. *Id.* at 3:17–19. "The mixture ratio of chitosan and fucoidan solutions is 0.5: 2.0." Sezer 4:5. Fucoidan microspheres range in size from 300-500 nm. *Id.* at 5:31.

FF2. Sezer teaches incorporating ofloxacin, a flouroquinolone group antibiotic, into one of the multi-particulate structures. *Id.* at 5:5.

[6] Final Office Action mailed May 17, 2016 ("Final Act.").

FF3. Examiner finds that ofloxacin is a cationic drug (i.e. having positive charge). Ans. 2.

FF4. Huan teaches "[a] pH stimuli-sensitive conjugate based on polyethylene glycol (PEG) with covalently attachment doxorubicin [DOX] via hydrazone bond (PEG-hyd-DOX)." Huan, Abstract. The PEG-hyd-DOX conjugate can target tumor tissues, inhibit tumor growth, as well as prolong the life of tumor-bearing mice when compared to using free DOX. *Id.* at 2.

Principle of Law

"If the claim extends to what is obvious, it is invalid under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007). "[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *Id.* at 416, citing *United States v. Adams*, 383 U.S. 39, 50–51 (1966).

Analysis

Appellant contends that Sezer's nanoparticles are structurally different than the nanogels presently claimed. Appeal Br. 8. Specifically, Appellant contends that the hydroxyl moieties of the nanoparticles of Sezer are "not free." *Id.* at 9; *see* Reply Br. 5. Appellant also contends that the sulfate moieties are bound and thereby not free. Appeal Br. 9; *see* Reply Br. 6. Thus, Appellant contends that Sezer's nanoparticles do not have free hydroxyl or sulfate moieties. Appeal Br. 8 ("[A]mphiphilic nanoparticles (e.g., having both hydrophobic and hydrophilic properties) do not have free

hydroxyl groups, and thus are not able to target cancer"). Specifically, Appellant contends that Sezer's chitosan-fucoidan hydroxyl or sulfate moieties are not free because the oppositely charged molecules are bound in the formation of the multiparticulate. *See id.* at 9 ("[T]he sulfate moieties of the nanoparticles of Sezer are bound (i.e. not free) to the positively charged moieties of the chitosan to form chitosan-fucoidan multiparticulates").

First, we observe that Appellant's argument – that the interaction between fucoidan and chitosan in forming multiparticulate structures results in an amphiphilic product having no charge – is a conclusory argument without supporting evidence, and is thereby unpersuasive. "Attorney's argument in a brief cannot take the place of evidence." *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). Second, we find that the Examiner made a *prima facie* case that the overall charge of the nanoparticle structure of Sezer is not neutral based on the evidence of record and sound reasoning, which Appellant failed to rebut. As the Examiner explained, "the presence of anionic and cationic groups does not mean that hydroxyl groups of fucoidan are not free." Ans. 5. We agree with Examiner that the evidence of record establishes that the overall charge of the nanoparticle structure of Sezer is not neutral. Sezer teaches that the nanoparticles contain a "mixture ratio of chitosan and fucoidan solutions is 0.5:2.0." FF1. The nanoparticles of Sezer therefore contain more fucoidan than chitosan. FF1. This supports Examiner's position that fucoidan is present in an amount sufficient to maintain the negative charge of the structure, including the presence of negatively charged hydroxyl groups.

Next, Appellant contends that Sezer does not demonstrate the efficacy of the fucoidan-chitosan particles nor is there evidence that the particles in combination with a drug demonstrated efficacy. *See* Appeal Br. 10.

We are not persuaded by the Appellant's efficacy argument. There is no requirement in the claim that the product is efficacious, all that is required is that it be "capable" of fulfilling the function. Claiming the product to have particular functionality shifts the burden to Appellant to show that the prior-art product could not satisfy that functionality. "A patent applicant is free to recite features of an apparatus [or product] either structurally or functionally. *See In re Swinehart*, 439 F.2d 210, 210 (CCPA 1971) ("There is nothing intrinsically wrong with [defining something by what it does rather than what it is] in drafting patent claims."). Yet choosing to define an element functionally, *i.e.*, by what it does, carries with it a risk. As our predecessor court stated in *Swinehart*:

> 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.

439 F.2d at 213; *see also*, *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

Here, Examiner explained that even though fucoidan-chitosan have opposite charges and therefore would be attracted to each other to form the particular nano structure, the evidence and Examiner's reasoning on this record suggests that not all available negative charges are occupied. *See* Ans. 5–6. Specifically, Examiner explains:

Although Sezer teaches incorporating two polymers of which

> one is anionic and the other is cationic (claim 1), the presence of anionic and cationic groups does not mean that hydroxyl groups [or sulfate moieties] of fucoidan are not free. There is no teaching in Sezer that the hydroxyl groups of fucoidan are not free. In the embodiment where fucoidan is paired with chitosan, although a fraction of the hydroxyl groups [as well as sulfate moieties] on fucoidan interact with the positively charged groups on chitosan, the hydroxyl groups are still free because the interaction with chitosan is ionic, which is a weak interaction that still leaves the hydroxyl groups available for further chemical interaction. As the hydroxyl groups are available for further chemical interaction, they are free.

Ans. 5–6. The same reasoning also applies to the sulfate groups. Examiner has provided a sound explanation, that Appellant did not rebut, as to why the fucoidan component of Sezer's particulate mixture would contain free hydroxyls as well as free sulfate groups and therefore there is sufficient reason to believe that the amount of free hydroxyls group is sufficient to bind P-selectin. *Compare In re Spada*, 911 F.2d 705 (Fed. Cir. 1990), *with In re Best*, 562 F.2d 1252, 1255 (CCPA 1977).

Appellant contends that their composition shows unexpected results. *See* Appeal Br. 10–12, *see id.* at 13–14; Reply Br. 12–13.

We agree with Examiner that Appellant's unexpected results argument with respect to the fucoidan-chitosan particles of Sezer is not persuasive. "The results [relied on by Appellant] show that fucoidan-DOX . . . show higher efficacy against B16F10 melanoma cells compared to the equivalent dosage of fucoidan, DOX, and DOX-PEG-DOX." Ans. 7. As explained by Examiner, "Sezer teaches that fucoidan particles provide sustained release of drugs encapsulated therein." Ans. 8.

> The results with which the actual difference was seen have been related with the controlled release of ofloxacin from the system.

> The release time was extended up to 6 days for fucoidan microspheres prepared at two different rpm rates, and while the effect of high amount drug release within the first hours called burst effect was decreased to 20%, this effect was decreased to 42% at most for the crosslinked chitosans, however it was seen that whole drug, was released within the first 8 hours in the non-crosslinked chitosan formulations. In addition, while it was seen that drug release for fucoidan microspheres complied with the 0 degree kinetic after the first 8 hours, for chitosan micro particles, such a release kinetic was not seen, on the contrary, for the crosslinked chitosan microspheres, a triphasic release profile was seen.

Sezer 5:17–27. As Examiner explains, the evidence provided in the Specification shows that, individually, DOX, fucoidan, and DOX-PEG-DOX are not as effective as the combination of fucoidan nanogel and DOX-PEG-DOX. Examiner finds that this is not unexpected because the combination of the fucoidan nanogel with the drug allows greater loading of the particle that is then released over time. "One would expect mice administered fucoidan-DOX to have a longer survival rate compared to mice administered DOX-PEG-DOX alone because fucoidan provides the feature of release of DOX over time, and DOX-PEG-DOX alone does not have this feature." Ans. 8. In other words, Examiner's position is that increased survival is an expected result of the sustained release formulation. *See* Ans. 8. We agree with Examiner's position that formulating a drug into a sustained release composition would result in the expected effect of providing the drug to the target over time. Accordingly, we agree with Examiner that the results provided in the Specification are expected results and thereby not sufficient to overcome the prima facie case of obviousness.

Appellant contends that Examiner's rejections are based on hindsight. *See* Appeal Br. 6; *see* Reply Br. 6.

We are not persuaded. Appellant has not directed us to what knowledge could only have been gleaned from the Specification and that was not available in the art relied on by Examiner in formulating the rejection.

> Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper.

In re McLaughlin, 443 F.2d 1392, 1395 (CCPA 1971).

In summary, we find the preponderance of evidence of record sufficient to support Examiner's conclusion that the composition as suggested by the combination of Sezer and Huan would be capable of targeting P-selectin. Appellant's secondary considerations of unexpected results were considered by Examiner but found to be unpersuasive. We have reviewed the same evidence and agree with Examiner that the evidence is insufficient to support of finding of unexpected results.

Accordingly, we affirm the obviousness rejection of claim 1. Appellant does not separately argue dependent claims 2–5, 7–13, and 30–32. Therefore, these claims fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

Obviousness over Sezer, Huan, and Chung

Claim 15 is dependent on claim 1 and further recites a fluorophore infra-red dye IR783. *See* Appeal Br. 21 (Claims Appendix). Appellant contends that Chung "fails to cure any deficiency of Sezer, alone or in combination." Appeal Br. 13.

Having found no error in the combination of Sezer and Huan, we are not persuaded by Appellant's intimation that Chung fails to make up for an alleged deficiency in the combination of Sezer and Huan. Accordingly, we affirm the rejection for the reasons set out by Examiner in the Final Office Action and Answer.

Obviousness over Sezer, Huan, and Zhang

Claim 14 is dependent on claim 1 and further recites a fluorophore. *See* Appeal Br. 21 (Claims Appendix). Appellant contends that in Zhang "the drugs are not conjugated to the [fucoidan extract] FE. . . . . Appellant submits that co-administering two free compositions will not result in the formation of a nanogel." Appeal Br. 14.

Zhang teaches "that fucoidan inhibits angiogenesis of melanoma" and other tumors. Zhang 82. "Since fucoidan has anti-tumor properties both *in vitro* and *in vivo*, a combination of fucoidan with chemotherapeutic drugs might be an intriguing option in the therapy of cancer patients." *Id.* Fucoidan extract from seaweed (Cladosiphon navae-caledoniae) consists of "mostly fucose (73%), xylose (12%) and mannose (7%). The ratio of sulfation was 14.5%." *Id.* at 92. Zhang discloses using a fluorescent component to monitor "generation of intracellular ROS, . . . [by measuring] cellular fluorescence intensity" over time. *Id.* at 94.

We are not persuaded by Appellant's contention that Zhang fails to teach a nanogel, because Examiner is not relying on Zhang for teaching fucoidan based nanogels. Examiner relies on the teachings of Sezer for disclosing nanogels/nanoparticles and teaching the incorporation of drugs for achieving extended release profile. *See* Ans. 7. Finding no error with

the Examiner's combination, we affirm the rejection for the reasons set out by Examiner in the Final Office Action and Answer.

SUMMARY

We affirm the rejection of claims 1–5, 7–13, and 30–32 under 35 U.S.C. § 103(a) over Sezer and Huan.

We affirm the rejection of claims 1–5, 7–13, 15, and 30–32 under 35 U.S.C. § 103(a) over Sezer, Huan, and Chung.

We affirm the rejection of claims 1–5, 7–14, and 30–32 under 35 U.S.C. § 103(a) over Sezer, Huan, and Zhang.

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