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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SUSANNA CUNNINGHAM-RUNDLES and
HONG LIN SMITH-JONES

Appeal 2017-004357
Application 12/688,160
Technology Center 1600

Before JEFFREY N. FREDMAN, DEBORAH KATZ, and JOHN G. NEW, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellants[1] seek our review, under 35 U.S.C. § 134(a), of the Examiner's decision to reject claims 18, 23, 27, 32, 43, and 44.[2] We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

Appellants' Specification is directed to using β-glucans, a component of the cell walls of yeasts, fungi, and bacteria, to expand hematopoietic progenitor cells, which can then be used for homing[3] and engrafting[4] to the bone marrow of a transplantation recipient. The Specification also explains that β-glucans can ameliorate the toxic effects of chemotherapy, while promoting development of neutrophils and their functional activity. (*See* Spec. 1:18–22.) Appellants focus on a specific β-glucan derived from maitake mushrooms ("MBG") in their claims.

Appellants' claim 18 recites[5]:

> A method of promoting homing of a population of cells which comprises hematopoietic progenitor and/or stem cells obtained from an umbilical cord blood sample from a donor mammal to the bone marrow of a recipient mammal, comprising
>
> orally administering a beta glucan composition, wherein said beta glucan composition is the D-fraction extracted from

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[1] Appellants report that the real party in interest is Cornell University. (Appeal Brief filed July 5, 2016 ("App. Br.") 2.)

[2] Appellants report that claims 1–18, 22–24, 27, 31–33, and 36–44 are pending, but that claims 1–17, 22, 24, 31, 33, and 36–42 have been withdrawn from consideration. (App. Br. 4.)

[3] Appellants' Specification defines "'homing'" as the ability of the transplanted cells to find their way to locate to bone marrow of the recipient. (Specification ("Spec.") 14:27–28.)

[4] Appellants' Specification defines "'engraftment'" as the ability of transplanted cells to integrate or insert into the bone marrow of the recipient. (Spec. 15:4–5.)

[5] Indentations added for clarity.

> maitake mushroom and characterized by a 1,6 main chain with 1,3 branches, and separately administering said population of cells to said recipient mammal.

(App. Br. 27, Claims App'x.) Appellants' independent claim 27 recites a method that is the same as the method recited in claim 18, but it is a method of "promoting *engraftment* of a population of cells which comprises hematopoietic progenitor and/or stem cells obtained from an umbilical cord blood sample from a donor mammal to the bone marrow of a recipient mammal" instead of a method of "homing" of a population of the same cells. (*See* App. Br. 27, Claims App'x (emphasis added).)

The Examiner rejected independent claims 18 and 27, as well as claims 23 and 32, which depend from them, under 35 U.S.C. § 103(a) as being obvious over Patchen,[6] Lin,[7] and Nanba,[8] as evidenced by Tanavde.[9] (Examiner's Answer issued November 15, 2016 ("Ans.") 3–9.) The Examiner also rejected claims 18, 23, 27, and 32 under 35 U.S.C. § 103(a) as being obvious over Cramer,[10] Lin, and Nanba, as evidenced by Tanavde. (Ans. 11–19.)

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[6] Patchen and Bleicher, US Patent No. 6,117,850, issued September 12, 2000.
[7] Lin et al., *Enhancement of Umbilical Cord Blood Cell Hematopoiesis by Maitake Beta-Glucan Is Mediated by Granulocyte Colony-Stimulating Factor Production*, 14 Clinical and Vaccine Immunology 21–27 (2007).
[8] Nanba and Kubo, US Patent No. 5,854,404, issued December 29, 1998.
[9] Tanavde et al., *Human stem-progenitor cells from neonatal cord blood have greater hematopoietic expansion capacity than those from mobilized adult blood*, 30 Experimental Hematology 816–823 (2002).
[10] Cramer, et al., *β-Glucan enhances complement-mediated hematopoietic recovery after bone marrow injury*, 107 Blood 835–840 (2006).

The Examiner rejected dependent claims 43 and 44 under 35 U.S.C. § 103(a) as being obvious over Patchen, Lin, and Nanba, as evidenced by Tanavde, and also in view of Kerre[11] (Ans. 9–11) or, alternatively, as being obvious over Cramer, Lin, Nanba, as evidenced by Tanavde, and Kerre (*id.* at 18–19).

Appellants do not argue for the separate patentability of any of the claims recited in these rejections.

Findings of Fact

1. Patchen teaches that methods for "enhancing or facilitating hematopoietic reconstitution or engraftment, by the administration of an underivatized, aqueous soluble β(1,3)-glucan." (Patchen 1:65–2:1; *see also* abstract.)

2. Patchen teaches that the methods can be used to increase the number of engrafted cells, to decrease the time to engraftment, or to enhance the quality of engraftment in hematopoietic reconstitution. (*See* Patchen 2:27–30.)

3. Patchen teaches that aqueous soluble β(l,3)-glucan can be administered to the patient at the time of autologous transplant to facilitate the reconstitution of hematopoietic progenitor cells. (Patchen 5:42–45.)

4. Patchen includes Example 11, which provides for administering underivatized, aqueous soluble β(1,3)-glucan to the patient at the time of

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[11] Kerre et al., *Both $CD34^+38^+$ and $CD34^+38^-$ Cells Home Specifically to the Bone Marrow of NOD/LtSZ scid/scid Mice but Show Different Kinetics In Expansion*, 167 The Journal of Immunology 3692–3698 (2001).

autologous transplant to facilitate reconstitution of the patient's hematopoietic progenitor cells. (*See* Patchen 10:4–14.)

5. Patchen does not teach promoting the homing or engraftment of umbilical cord blood sample cells or using β(1,3)-glucan with 1,6 main chain with 1,3 branches maitake mushroom extract.

6. Lin teaches that umbilical cord blood cells are increasingly used for stem cell transplantation for the treatment of leukemia. (*See* Lin 21.)

7. Lin teaches that maitake β-glucan ("MBG") enhances human umbilical cord blood cell proliferation and differentiation. (*See* Lin 21.)

8. Lin states that the results reported raise the possibility that MBG could enhance the expansion of umbilical cord blood cells *ex vivo* to improve engraftment. (*See* Lin 21.)

9. Tanavde teaches that neonatal (umbilical) cord blood preparations generated massively increased *in vitro* assessed hematopoietic capacity and maintained engraftment potential compared to peripheral blood stem cells, which generated less *in vitro* assessed hematopoietic capacity and decreased engraftment potential. (Tanavde abstract.)

10. Nanba teaches that it was known that polysaccharides consisting of β-1,6-linked glucose main chain with β-1,3-linked glucose branches, as well as β-1,3-linked glucose main chain with β-1,6-linked glucose branches, extracted from the fruit bodies of Grifola (maitake) mushrooms have anticancer activity. (*See* Nanba 1:11–15.)

11. Nanba teaches extracting antitumor substances with immunopotentiating activity from Grifola. (Nanba 1:38–42.)

12. Nanba teaches that the substance obtained by the invention is of low toxicity and high safety and can be administered orally in foods and

pharmaceutical preparations, especially antitumor agents as tablets, capsules, liquids, or syrups. (*See* Nanba 4:34–38.)

13. Cramer teaches the effect of orally administered whole glucan particles (such as β-glucan) on the repopulation of bone marrow in lethally irradiated mice following hematopoietic transplantation. (Cramer 838.)

14. Cramer teaches that mice treated with β-glucan after irradiation and subsequent hematopoietic transplantation had approximately 40% more day-12 colony forming unit-S colonies in the spleen compared with mice without β-glucan treatment. (Cramer 838).

15. Cramer teaches that CR3, the binding site of β-glucan, may contribute to early engraftment of hematopoietic cells. (*See* Cramer 838.)

16. Cramer teaches that yeast β-glucan may assist in the engraftment of hematopoietic cells and the acceleration of hematopoietic function following allogenic hematopoietic transplantation. (*See* Cramer 840.)

Analysis

Rejection over Patchen, Lin, Tanavde, and Nanba

The Examiner determines that it would have been obvious to one of ordinary skill in the art to substitute hematopoietic stem progenitor cells and bone marrow cells in the methods of Patchen with umbilical cord cells, because Lin and Tanavde teach that umbilical cord cells can be used for stem cell transplantation and expand well *ex vivo*. (*See* Ans. 6–7; *see* FFs 6–9.) The Examiner also determines that a person of ordinary skill in the art would have been motivated to substitute the MBG composition from Lin or Nanba for β-glucan composition of Patchen, because Lin and Nanba teach that MBG is widely known to treat cancer and can be administered orally to

activate antitumor response through effects on the immune system. (*See* Ans. 7–8; FFs 7, 8, and 10–12.) The Examiner determines further that a person of ordinary skill in the art at the time would have used the MBG composition with 1,6 main chain and 1,3 branches taught in Nanba because it was known to enhance murine bone marrow cell proliferation and differentiation and for using progenitor and stem cells in cancer therapies. (Ans. 7–8.)

Appellants argue that the Examiner erred in rejecting claims 18, 23, 27, and 32 as being obvious over Patchen, Lin, and Nanba, as evidenced by Tanavde because the skilled artisan would not have considered Patchen to teach that oral administration of beta glucan promotes cell homing and engraftment. (*See* App. Br. 9–11; *see* Reply Brief filed January 17, 2017 "Reply Br." 2.) Rather, Appellants argue, a skilled artisan would have understood that Patchen teaches mobilization of bone marrow cells into the blood for collection and saving the stem/progenitor cells for re-transfusion back into the subject after chemotherapy. (*See* App. Br. 10.)

We are not persuaded by Appellants' argument because, in addition to teaching that administration of β-glucan promotes mobilization, Patchen also teaches in Example 11, and in other passages, administering β-glucan "at the time of autologous transplant to facilitate the reconstitution of hematopoietic progenitor cells." (Patchen 10:8–12, Example 11; *see* Ans. 4; *see also* Final Office Action issued October 5, 2015 at 4.) We do not disagree with Appellants that mobilization of cells in the bone marrow is a separate and distinct process from homing or engraftment (*see* App. Br. 10), but Appellants do not address Example 11 and other portions of Patchen that discuss the effects of β(1,3)-glucan on reconstitution of hematopoietic cells

in their arguments. (*See, e.g.*, Patchen 1:65–67 ("The invention further relates to methods for enhancing or facilitating hematopoietic reconstitution or engraftment, by the administration of an underivatized, aqueous soluble β(1,3)-glucan.").) We are not persuaded, as Appellants argue, that Patchen teaches *only* an effect that is opposite to the effect of the claimed methods. (*See* App. Br. 10.)

We are also not persuaded that Appellants' claimed methods are nonobvious because the mobilization methods of Patchen requires intravenous injection of β-glucan, not oral delivery. (*See* App. Br. 12.) According to Appellants, the teaching in Patchen that β-glucan can be administered by many different routes refers only to mobilization protocols because the summary of the invention and Examples 1–10 are directed to mobilization. (*See id.*)

However, immediately prior to teaching that β-glucan can be administered by many routes, Patchen states: "The underivatized, aqueous soluble β(1,3)-glucan is administered to an animal or a human in an effective amount, sufficient to mobilize [peripheral blood precursor cells], to elevate the level of circulating [peripheral blood precursor cells] *or facilitate hematopoietic reconstitution*." (Patchen 4:39–42 (emphasis added).) Patchen continues by referring to dosing regimens and then to oral administration along with other routes. (*See* Patchen 4:43–60.) Thus, we do not agree with Appellants that reference to oral administration is specific only to mobilization; instead, we understand that it also refers to hematopoietic reconstitution. Because Patchen teaches enhancing or facilitating hematopoietic reconstitution or engraftment, we are not persuaded that this element renders Appellants' claims non-obvious.

Appellants argue that Lin teaches using MBG to expand umbilical cord cells *in vitro* and that it was only conjecture and hindsight construction by the Examiner to conclude that there would have been a reasonable expectation of success using MBG with the *in vivo* methods of Patchen. (*See* App. Br. 16–17.) We are not persuaded by Appellants' argument because the conclusions stated in Lin indicate a reasonable expectation that the *in vitro* results might be successfully applied to other settings. Lin states: "the results support the possibility that MBG could enhance the expansion of [cord blood] cells ex vivo to improve engraftment." (Lin 21.) Thus, the conclusions recited in Lin support the Examiner's determination.

Appellants also argue that the activity of β-glucan is highly unpredictable, wherein β-glucan derived from different sources, for example fungi or yeast, can have significantly different effects *in vivo*. (*See* App. Br. 17–20; *see* Reply Br. 3.) Appellants cite to Driscoll,[12] arguing that yeast-derived β-glucan exhibits stronger anti-tumor activity than fungus-derived β-glucan. (*See* App. Br. 17.) Appellants also cite to Hishida[13] to argue that β-glucans from mushroom fruit bodies were inactive when administered orally, but had anti-tumor effects when administered intraperitoneally or intravenously. (*See* App. Br. 17–18.) Appellants argue that Nanba teaches only *in vitro* experiments and intraperitoneal injection of glucan/protein

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[12] Driscoll et al., *Therapeutic potential of various β-glucan sources in conjunction with anti-tumor monoclonal antibody in cancer therapy*, 8 Cancer Biology & Therapy 218–225 (2009).
[13] Hishida et al., *Antitumor Activity Exhibited by Orally Administered Extract from Fruit Body of Grifola frondosa (Maitake)*, 36 Chem. Pharm. Bull 1819–1827 (1988).

complexes to demonstrate immunopotentiating and anti-cancer activity. (*See* App. Br. 18.)

Because the results in Lin "support the possibility that MBG could enhance the expansion of [cord blood] cells ex vivo to improve engraftment" (Lin 21), we are not persuaded by Appellants' argument. Lin expressly suggests using MBG *ex vivo*, even though the actual results it reports are from *in vitro* studies. Lin also reports that "MBG administered orally activates the host antitumor response through effects on the immune system rather than by direct cytostatic or cytotoxic effects on tumor cells." (Lin 21.) Furthermore, even though β-glucans from different sources can have different effects, as indicated by Driscoll and Hishida, Lin addresses the specific β-glucan recited in Appellants' claims. (*See* Ans. 25.) Accordingly, we are not persuaded that one of ordinary skill in the art would not have looked to MBG for oral administration to promote homing and engraftment of umbilical cord blood cells.

Appellants argue that "[a]gainst the unpredictability in the art . . . the results achieved by this present invention are unexpected." (App. Br. 19; *see also* Reply Br. 5.) Appellants cite to page 11, lines 23–28 to page 12, lines 1–24 and Figures 3–5 of their Specification. (*See* App. Br. 19.) Although Figures 3–5 provide results comparing treatment with MBG and without, pages 11 and 12 do not discuss results, but rather the sources and composition of materials. Appellants do not direct us to, and we do not find, discussion characterizing of the results shown in Figures 3–5 as being unexpected. Instead, Appellants' argument is merely unsupported attorney argument, to which we accord little probative value. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) (holding that attorney arguments and

conclusory statements that are unsupported by factual evidence are entitled to little probative value.

Appellants do not persuade us that the Examiner erred in rejecting claims 18, 23, 27, and 32 as being obvious over Patchen, Lin, and Nanba, as evidenced by Tanavde.

Rejection over Cramer, Lin, Tanavde, and Nanba

Cramer teaches that yeast β-glucan may assist in the engraftment of hematopoietic progenitor cells and the acceleration of hematopoietic function following allogeneic transplant. (*See* Cramer 840; FFs 13–16; *see* Ans. 13.) The Examiner determines that because Lin, as further evidenced by Tanavde, indicates umbilical cord cells were used for stem cell transplantation, it would have been obvious to those of ordinary skill in the art at the time to substitute the hematopoietic progenitor cells used in Cramer with umbilical cord blood cells. (*See* Ans. 15–16.) The Examiner also determines that a person of ordinary skill in the art would have substituted the β-glucan used in Cramer with the MBG taught in Lin and Nanba because MBG was known to be a useful cancer treatment and enhances murine bone marrow cell proliferation and differentiation. (Ans. 16–17.)

Appellants argue that Cramer teaches using β-glucans distinct from those claimed. (*See* App. Br. 21.) We are not persuaded by this argument because it does not address the Examiner's entire rejection, which includes citations to Lin and Nanba showing that maitake β-glucan characterized by a 1,6 main chain with 1,3 branches was suggested to enhance the expansion of umbilical cord blood cells *ex vivo* to improve engraftment. (*See* Ans. 5.) "Non-obviousness cannot be established by attacking references individually

where the rejection is based upon the teachings of a combination of references." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986).

Appellants also argue that Driscoll teaches away from substituting the whole glucan particles ("WGP") used in Cramer with the MBG taught in Lin and Nanba because Driscoll teaches that yeast-derived β-glucan WGP have much stronger adjuvant activity compared to mushroom β-glucans with respect to anti-cancer activity. (*See* App. Br. 22, citing Driscoll 219.) We are not persuaded by this argument because the portion of Driscoll cited by Appellants refers to *adjuvant* activity of β-glucans when used in combination with a monoclonal antibody to achieve tumor regression. Appellants do not claim adjuvant activity of β-glucan.

Appellants do not persuade us that the Examiner erred in rejecting claims 18, 23, 27, and 32 as being obvious over Cramer, Lin, and Nanba, as evidenced by Tanavde.

Rejections of Claims 43 and 44

The Examiner rejected claims 43 and 44 as being obvious over either Patchen or Cramer, Lin, Nanba, and Kerre in view of Tanavde. (*See* Ans. 9–11 and 18–19.) Claims 43 and 44 depend from claims 18 and 27, respectively, and require the population of cells obtained from the umbilical cord blood to be administered to the recipient without *in vitro* expansion. (*See* App. Br. 28, Claims App'x.) The Examiner cites Kerre for teaching injection of umbilical cord blood cells into a recipient mouse within 24 hours of collection, without *in vitro* expansion. (*See* Kerre 3693; *see* Ans. 10.)

Appellants argue that Kerre does not teach oral administration of any β-glucan and does not alleviate the deficiencies of the combination of

Patchen, Lin, and Nanba or of Cramer, Lin, and Nanba. (*See* App. Br. 23.) Because, as explained above, we are not persuaded that there are deficiencies in the combination of Patchen or Cramer, Lin, and Nanba, Appellants have not persuaded us that the Examiner's rejection of claims 43 and 44 is an error.

Appellants do not persuade us that the Examiner erred in rejecting claims 43 and 44 as being obvious over Patchen or Cramer, Lin, Nanba, and Kerre, as evidenced by Tanavde.

Conclusion

Upon consideration of the record and for the reasons given, the rejection of claims 18, 23, 27, 32, 43, and 44 under 35 U.S.C. § 103(a) is sustained.

Therefore, we affirm the decision of the Examiner.

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

AFFIRMED