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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CHRISTOPHER J. CENTENO

Appeal 2019-006371
Application 15/891,852
Technology Center 1600

Before DONALD E. ADAMS, ULRIKE W. JENKS, 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 of culturing nucleated cells harvested from a patient and selecting viable mesenchymal stem cells (MSC) for implantation. 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(a). Appellant identifies Regenexx, LLC as the real party in interest. Appeal Br. 1.

STATEMENT OF THE CASE

The Specification describes "methods for facilitating repair in a damaged avascular site, for example an intervertebral disc; more particularly, the invention provides applying environmentally conditioned autologous stem cells . . . to avascular sites in patients in need thereof." Spec. ¶1. The Specification explains that MSC may be "harvested and expand[ed] . . . under various atmospheric conditions that simulate a damaged disc's environment." *Id.* ¶61.

> In some cases the harvested stem cells are cultured under 3 to 10% oxygen and in other cases the harvested stem cells are cultured under 3 to 7% oxygen. These lower oxygen conditions replicate the hypoxic conditions present in typical damaged disc environments. . . . Selection occurs as cells are cultured, with viable cells that are able to survive and ultimately expand having an advantage when implanted into a disc having a hypoxic environment.

Id.

Claims 5–25 are on appeal and can be found in the Claims Appendix of the Appeal Brief. Claims 5 and 25 are illustrative of the claims on appeal. They read as follows:

> 5. A method for treating an avascular zone in a patient in need thereof, the method comprising:
>
> culturing nucleated cells harvested from the patient in need thereof in a culture medium under a selective pressure of about 1% to about 10% oxygen for 1–28 days;
>
> selecting viable mesenchymal stem cells capable of growth in the culture medium under the selective pressure of about 1% to about 10% oxygen; and
>
> providing the selected, viable mesenchymal stem cells for implantation in the avascular zone.

> 25. A method for treating an avascular zone in a patient in need thereof, the method comprising:
>
> first culturing nucleated cells harvested from the patient in need thereof in a culture medium under a selective pressure of about 1% to about 10% oxygen for 1–28 days;
>
> subsequent to the first culturing, selecting viable mesenchymal stem cells capable of growth in the culture medium under the selective pressure of about 1% to about 10% oxygen; and
>
> providing the selected, viable mesenchymal stem cells for implantation in the avascular zone.

Appeal Br. 23, 26.

Appellant seeks review of the following rejections:[2]

I. Claims 5–7, 12–14,[3] and 18–25 under 35 U.S.C. § 103 as unpatentable over Centeno[4] and Grayson;[5]

II. Claims 8 under 35 U.S.C. § 103 as unpatentable over Centeno, Grayson, and Ma;[6]

III. Claims 8 and 9 under 35 U.S.C. § 103 as unpatentable over Centeno, Grayson, and Kolesnikova;[7]

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[2] The obviousness-type double patenting rejection of claims 1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, and 86 referred to Examiner's Answer (*see* Ans. 15) was withdrawn prior to the appeal in an Advisory Action mailed January 2, 2019.

[3] It is clear that Examiner included claim 14 in the obviousness rejection of these claims. *See* Final Act 5 (referring to claim 14). We likewise interpret the Appeal Brief to include claim 14 in the arguments Appellant makes regarding this rejection.

[4] WO 2007/087519 A2, published Aug. 8, 2007 ("Centeno").

[5] Warren L. Grayson et al., *Effects of Hypoxia on Human Mesenchymal Stem Cell Expansion and Plasticity in 3D Constructs*, 207 J. of Cellular Physiology 331–339 (2006) ("Grayson").

[6] US 6,875,605 B1, issued April 5, 2005 ("Ma").

[7] RU 2323252, published April 27, 2008 ("Kolesnikova").

IV. Claim 10 under 35 U.S.C. § 103 as unpatentable over Centeno, Grayson, and Toner;[8]

V. Claims 11 and 22 under 35 U.S.C. § 103 as unpatentable over Centeno, Grayson, and Schallmoser;[9]

VI. Claims 15–17 under 35 U.S.C. § 103 as unpatentable over Centeno, Grayson, Binette,[10] and Bennett;[11] and

VII. Claims 5–25 as provisionally rejected for obviousness-type double patenting over claims 70–75, 77, 78, and 80–86 of U.S. Patent Application No. 13/132,840 (the "'840 Application").

Appeal Br. 8.

I. OBVIOUSNESS REJECTIONS I–VI

Issue

All of Examiner's obviousness rejections are premised on the same combination of Centeno and Grayson. Appellant does not present separate arguments for Rejections II–VI, but instead relies on the same arguments it presents for claim 5 in the first rejection. *See* Appeal Br. 18–21. Accordingly, we consider the obviousness rejections together in our analysis. We select claim 5 as representative of claims 6–24, which are not argued separately from claim 5. *See* 37 C.F.R. § 41.37(c)(1)(iv). The issue for these rejections is whether a preponderance of the evidence supports Examiner's conclusion that cited prior art renders the method of claim 5

[8] US 2004/0248293 A1, published Dec. 9, 2004 ("Toner").
[9] Katharina Schallmoser et al., *Human Platelet Lysate Can Replace Fetal Bovine Serum for Clinical-scale Expansion of Functional Mesenchymal Stromal Cells*, 47 Transfusion 1436–46 (2007) ("Schallmoser").
[10] US 2005/0038520 A1, published Feb. 17, 2005 ("Binette").
[11] US 2003/0198687 A1, published Oct. 23, 2003 ("Bennett").

obvious. In addition to its arguments regarding claim 5, Appellant presents a separate argument for claim 25 that we likewise address below.

Findings of Fact

FF1. Centero teaches methods for autologous transplantation of MSCs and progenitor helper cells (PHC) "from bone marrow to degenerated intervertebral discs or joints." Centero ¶ 17; Abstr. In particular, Centero teaches "a[ ]procedure where target cells are harvested, then isolated, then reimplanted into a target site, all from and into the same patient." *Id.* ¶ 17.

FF2. Centero also teaches experimental techniques

> to determine which bone marrow cells should be removed via negative selection to generate a MSC/PHC population most likely to regenerate certain tissue types in-vitro as well as which combination of fibrinogen and hyaluronic acid and which degree of gel maceration provides the best matrix for in-vitro and in-vivo regeneration of joints and intervertebral discs.

Centero ¶ 18.

FF3. According to Centero,

> physicians will be unlikely to utilize regenerative techniques unless the isolation can be easily performed by operating room staff and the isolation itself can be performed during the same surgical procedure as the actual transplantation. If expansion of the cells is required for success, then that expansion would preferably be carried out in a hospital or clinical lab and not a research laboratory.

Centero ¶ 5; *see also id.* ¶ 7 (distinguishing prior art methods as "not practical for surgeons and hospitals" or "a clinical or hospital lab without experienced research personnel"). Thus, Centero teaches that its method is "designed to be used by operating room staff . . . during the same surgical procedure as transplantation." *Id.* ¶ 17; Abstr. However, Centero also

teaches that "[t]he method can be used as a two step procedure where cells are harvested, then isolated, then reimplanted at a later time." *Id.* at Abstr.

FF4. For example, Centero describes "an alternative embodiment" wherein "the cell sample may be separated using the same combination of cell surface antigens determined through experimental design discussed herein, with flouresence activated cell sorting being utilized." Centero ¶ 27. Centero teaches "[t]his alternative selection method may be performed at an on or off-site clinical lab." *Id.*

FF5. Centero also teaches that "[a]lternatively, the cells selected as most likely to regenerate the target tissue may be expanded in a hospital lab before re-injection." Centero ¶ 28.

FF6. Grayson describes results from experiments in which human mesenchymal stem cell (hMSC) "were cultured under physiologically relevant oxygen environments (2% O_2) in three-dimensional (3D) constructs for up to 1 month in order to investigate the combined effects of chronic hypoxia and 3D architecture on hMSC tissue development patterns." Grayson, 331. Grayson teaches that hMSC cultured and expanded under these hypoxic conditions "exhibited an extended lag phase in order to acclimatize to culture conditions," but

> subsequently proliferated continuously throughout the culture period, while maintaining significantly higher colony-forming unit capabilities and expressing higher levels of stem cell genes than hMSC cultured at 20% O_2 (normoxic) conditions. Upon induction, hypoxic hMSC also expressed higher levels of osteoblastic and adipocytic differentiation markers than normoxic controls. . . . Importantly, hMSC maintained the ability to thrive in prolonged hypoxic conditions suggesting that hypoxia may be an essential element of the in vivo hMSC niche.

Id; see also id. at 338 (reporting that "hMSC in vitro proliferation is actually enhanced by long-term chronic hypoxia" and "[o]ur results demonstrate that hMSC cultured at 2% O_2 maintain much higher colony forming numbers than cells cultured at 20% O_2").

FF7. Grayson teaches that colony-forming unit "numbers in hypoxic cultures were also higher than those of the original cell population seeded into the matrices indicating that the more primitive cells are being selected by oxygen deprivation." Grayson, 338.

Analysis

Claims 5–24

Examiner finds that Centero "teaches a therapeutic method for selecting autologous MSCs for administration to a degenerated intervertebral disc" in which the cells may "be expanded in a hospital lab before re-implantation." Final Act. 3–4. Examiner acknowledges that Centero "is silent with regard to the culture conditions . . . for expansion of the selected MSCs," but finds that Grayson teaches culturing and expanding MSCs under hypoxic conditions as recited in claim 5 "displayed significantly improved expansion characteristics while maintaining their multi-lineage potential." *Id.* at 4. Thus, Examiner determines

> one of ordinary skill in the art would have been motivated to use 2-5% oxygen and 5% carbon dioxide for the culture of MSCs in the method of Centeno '519 because Grayson et al teach that these percentages provide improved expansions characteristics for MSCs. The culturing of the MSCs under hypoxic conditions would also provide for the selection of MSCs capable of surviving under low oxygen conditions after culturing for at least one day. One of ordinary skill in the art would have had a reasonable expectation of success because Grayson teach that hypoxic conditions select for MSCs that are

> more primitive with a higher CFU-F number that correlates with high in vitro lifespan and extended proliferation.

Id. at 4–5.

We adopt the Examiner's findings and reasoning regarding the scope and content of the prior art (Final Act. 3–5; FF1–FF7) and agree that claim 5 is obvious over the articulated combination of Centero and Grayson. We address Appellant's arguments below.

Appellant argues that Examiner's combination of Centero and Grayson is "actively discouraged by Centero." *See* Appeal Br. 10–16. More specifically, Appellant contends that Examiner's finding that Centero "teaches a therapeutic method that selects and expands MSCs is based on a single sentence . . . that generally discusses expanding cells (paragraph [0028]) but which runs contrary to the entirety of the remaining teaching of the reference and its objectives." *Id.* at 10. Appellant urges that "read as a whole" Centero "provides no motivation for adding an *in-vitro* culturing step" and that "by relying on a single statement in Centero '519 that conflicts with the entirety of the remaining teachings of Centero '519, the Office has engaged in improper hindsight analysis." *Id.* at 14–15 (citing *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986) ("*Bausch & Lomb*")).

Appellant's argument is unpersuasive. As an initial matter, Centero does not actively discourage expanding MSCs prior to implanting them. To the contrary, Centero describes a method that includes an expansion step in a lab (i.e., *in vitro*) as an "alternative[]" embodiment of Centero's invention. FF5. It is true that in some instances Centero expresses a preference for a selection method that can be practiced by operating room staff as part of the

same procedure. Centero ¶¶ 5, 7, 17. However, there are also multiple instances in which Centero makes clear that its methods also encompass "two step" procedures in which cells are harvested and reimplanted at a later time. *See* FF3–FF5. For example, Appellant quotes a portion of Centero paragraph 5 as evidence that Centero "clearly intends for its . . . methods to be performed as a single procedure . . . not over multiple days as would be required if a culturing step were included in the Centero" process. Appeal Br. 11. But the ultimate sentence in paragraph 5, which Appellant does not quote in its brief, expressly contemplates instances in which "expansion of the cells is required for success" and thus would be carried out in a lab—not the operating room. FF3. In addition, Centero describes other embodiments in which at least portions of the selection method are performed in a laboratory. FF4. Thus, we disagree with Appellant's position that only a "single sentence" in Centeno paragraph 28 (*see* Appeal Br. 10) supports Examiner's finding Centeno teaches a culturing and expanding step in its method.

Rather, read as a whole, Centero teaches a preferred embodiment in which the harvesting, selection, and implantation of MSCs occurs in a single procedure as well as alternative "two step" embodiments "where cells are harvested, then isolated, then reimplanted at a later time." FF3. It is as part of these two step embodiments that Centero teaches that MSCs may "alternatively" be cultured and expanded before implantation. FF5.

As such, the facts here are very different from those in *Bausch & Lomb*. There, the district court relied on a "single line" out of the specification, stating that one way in which a particular objective could be achieved was by the use of a laser. 796 F.2d at 448. However, "the

immediately following sentences" noted that the use of a laser "is limited by several disadvantages" and that instead the author "suggests the use of a special class of polymer" to achieve the same objective. *Id.* As such, the Federal Circuit determined "[a] complete reading demonstrates quite clearly that [the author] is setting up a strawman and point out its disadvantages to highlight the advantages of [the author's] invention, that special class of polymers." *Id.* But unlike *Bausch & Lomb*, Centero paragraph 28 is not setting up a strawman to distinguish its invention; rather paragraph 28 describes an alternative embodiment of Centero's invention.

We are not persuaded by the testimony in the Declaration of Joseph C. Maroon, dated August 27, 2018 ("Maroon Decl.") and the Declaration of Christopher J. Centeno, dated August 27, 2018 ("Centeno Decl."). Both declarations rely on the same teachings in Centeno paragraphs 5, 7, and 17 to conclude that the teaching in paragraph 28 are inconsistent and therefore that they would "disregard the statement in paragraph [0028]" if they were reading Centero for "instructive purposes." Maroon Decl. ¶¶ 12, 15; Centeno Decl. ¶¶ 13, 16. The problem with the testimony in both of these declarations is that it cannot be reconciled with the statements in Centeno teaching "two step" embodiments. FF3–FF5; *see also PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1361 (Fed. Cir. 2007) (holding the jury's determination of non-obviousness was not supported by the testimony of patentee's expert because "[t]he problem with [the expert's] testimony about the prior art references is that it cannot be reconciled with . . . the prior art references themselves"). Indeed, neither Appellant, nor its declarants, even attempt to reconcile paragraph 28 with their arguments as to what the rest of Centero discloses. We, however, decline Appellant's

invitation to disregard paragraph 28 because doing so would conflict with Centero's various disclosures regarding "two step procedure[s]" (*see* FF3–FF5) and is contrary to precedent. *See Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 807, 10 USPQ2d 1843, 1846 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976) ("[I]n section 103 inquiry . . . 'all disclosures of the prior art, including unpreferred embodiments, must be considered.'").

For these reasons, we determine the preponderance of the evidence supports Examiner's rejection of claim 5 and therefore affirm. We affirm the rejection of claims 6–24 for the same reasons.

Claim 25

In addition to the arguments concerning claim 5, which we determine are unpersuasive for the reasons explained above, Appellant argues that Centeno "clearly requires obtaining a specific population of cells comprising MSCs via a first selecting step, which is exactly opposite the limitations of claim 25 that recites a first culturing step followed by a selection step." Appeal Br. 17–18.

We are not persuaded by Appellant's additional argument for claim 25. As Examiner correctly points out, "a selection step prior to culturing is not excluded from claim 25 due to the transitional phrase of 'comprising'" and "culturing the nucleated cells under hypoxic conditions is itself a selection step as it only allows for MSCs (which are nucleated cells) capable of surviving under these conditions to remain viable for collections upon its conclusion." Ans. 12; FF6–FF7. Thus, the combination of Centero's harvesting and expansion steps with Grayson's hypoxic culturing and selection conditions, as articulated by Examiner, reads on the method of

claim 25. *See* FF1–FF7. This is true even if another selection step is performed prior to culturing and subsequently selecting the MSCs under hypoxic conditions.

Accordingly, we likewise determine that the rejection of claim 25 is supported by a preponderance of the evidence.

II. PROVISIONAL DOUBLE PATENTING REJECTION

In addition to the above rejections, Examiner provisionally rejected claims 5–25 for ODP over certain claims of Appellant's co-pending '840 Application. Final Act. 15. Appellant argues the rejection is "premature" and asks that the rejection be "withdrawn or stayed" at least until the claims of the '840 Application "issue as a patent." Appeal Br. 21.

Appellant does not, however, present any argument that claims 5–25 are patentably distinct from the claims of the '840 Application identified in Examiner's rejection. Appellant also did not file a terminal disclaimer to moot this rejection. Thus, on this record, Appellant has not contested the merits of Examiner's provisional ODP rejection.

"If a ground of rejection stated by the examiner is not addressed in the appellant's brief, appellant has waived any challenge to that ground of rejection and the Board may summarily sustain it." MPEP § 1205.02 (9th Ed., Rev. 08.2017 (Jan. 2018)).

For the foregoing reasons, we summarily affirm this rejection.

DECISION SUMMARY

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
5–7, 12–14, 18–25	103	Centeno, Grayson	5–7, 12–14, 18–25	
8	103	Centeno, Grayson, Ma	8	
8, 9	103	Centeno, Grayson, Kolesnikova	8, 9	
10	103	Centeno, Grayson, Toner	10	
11, 22	103	Centeno, Grayson, Schallmoser	11, 22	
15–17	103	Cenento, Grayson, Binette, Bennett	15–17	
5–25		Provisional Obviousness-type Double Patenting	5–25	
Overall Outcome			5–25	

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