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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HUI XU, WENDELL SUN, CUNQI CUI, and HUA WAN

Appeal 2019-06096
Application 12/956,058
Technology Center 1600

BEFORE DONALD E. ADAMS, ELIZABETH A. LAVIER, and TAWEN CHANG, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from Examiner's decision to reject claims 17–21, 25–26, and 28–37 (Appeal Br. 2). 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 the real party in interest as "LifeCell Corporation" (Appellant's January 17, 2019 Appeal Brief (Appeal Br.) 1).

STATEMENT OF THE CASE

Appellant's disclosure relates to, *inter alia*, "a device for treating a nerve . . ., comprising an arterial tissue matrix, wherein substantially all of the native cells have been removed" (Spec. ¶ 5). Claim 17 is reproduced below:

> 17. An implantable device for treating a nerve, comprising:
>
> an arterial tissue matrix having substantially all of the native cells removed, having exogenous mesenchymal stem cells added to the arterial tissue matrix, wherein the exogenous mesenchymal stem cells added to the arterial tissue matrix improve repair, regrowth, and regeneration of nerve and muscle tissue compared to arterial tissue matrix alone when the arterial tissue matrix is implanted across a defect in a nerve;
>
> wherein the shape of the arterial tissue matrix is a conduit;
>
> and wherein the implanted conduit is capable of allowing a peripheral nerve to grow therethrough.

(Appeal Br. 16.)

Claims 17–21, 25, 26, and 28–37 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of McFetridge,[2] Siemionow,[3] Hadler,[4] and Ayares.[5]

[2] McFetridge, US 2006/0282173 A1, published Dec. 14, 2006.
[3] Siemionow et al., WO 2009/124170 A1, published Oct. 8, 2009.
[4] Hadler et al., *Ultrastructure of a hyaluronic acid matrix*, 79 Proc. Natl. Acad. Sci. USA 307-09 (1982).
[5] Ayares et al., US 2005/0260176 A1, published Nov. 24, 2005.

ISSUE

Does the preponderance of evidence relied upon by Examiner support a conclusion of obviousness?

FACTUAL FINDINGS (FF)

FF 1. McFetridge discloses:

> [A]n implantable device that includes a tissue graft comprising a substantially decellularized umbilical vessel having a luminal surface and an ablumenal surface. The substantially decellularized umbilical vessel is prepared by an automated dissection process and is not substantially cross-linked. The substantially decellularized umbilical vessel may be capable of having at least one cell type seeded on at least a portion of at least one of the luminal and ablumenal surfaces thereof. The umbilical vessel may be an umbilical vein or an umbilical artery, and may be from a mammal, such as but not limited to, a human.

(McFetridge ¶ 16; *see id.* ¶ 4 (McFetridge "relates to implantable devices for tissue engineering, and more particularly but not by way of limitation, to substantially decellularized grafts from umbilical cord vessels for use in tissue engineering as a substantially acellular matrix and for use with cell seeding methodology."); Final Act. 5; *see also* Final Act. 6 (citing McFetridge ¶¶ 91 and 134; Hadler 307) (Examiner finds that McFetridge discloses that its arterial tissue matrix includes hyaluronic acid, a glycosaminoglycan.).)

FF 2. McFetridge discloses:

> The term "substantially decellularized" . . . mean[s] that physical, chemical, or enzymatic means, or any combination thereof, has substantially or completely removed the cellular component of vascular tissue thereof. The remaining substantially decellularized vascular tissue comprises the extracellular matrix of the native vascular tissue and may include, but is not limited to, elastin, collagen, fibrin, and other

> extracellular proteins or non-proteinaceous compounds found in vascular tissue, or any combination thereof known to one of ordinary skill in the art.

(McFetridge ¶ 76; *see* Final Act. 6.)

FF 3. McFetridge discloses that its device may be seeded with "at least one cell type on the substantially decellularized umbilical vessel, wherein the at least one cell type is selected from the group consisting of smooth muscle cells, fibroblasts, endothelial cells, keratinocytes, myogenic cells, stem cells, muscle cells, epithelial cells, any other applicable cell type lineages, and combinations thereof" (McFetridge ¶ 21; *see id.* ¶ 176 (McFetridge discloses that "cells will be seeded inside a bioreactor on the ablumenal side, and media will be flushed inside. Thus the cells will integrate the matrix and be fed by the media diffusion through the scaffold from the lumen flow."); *id.* ¶ 104; Final Act. 5 (Examiner finds that McFetridge's implantable device comprises "exogenous cells added to . . . [its] arterial tissue matrix."); Final Act. 5–6; Final Act. 7 (citing McFetridge ¶ 81) (Examiner finds that McFetridge discloses the use of an "arterial tissue matrix is derived from a pig," i.e. exogenous (allogenic) cells.).

FF 4. McFetridge discloses that its implantable device can be used for, *inter alia*, nerve regeneration (McFetridge ¶ 104; *see* Final Act. 5).

FF 5. McFetridge discloses that "[f]or peripheral nerve grafts a favorable environment for nerve growth placed in the gap of the injury will permit regeneration. The tubular structure of the scaffold along with nerve growth factor and Schwann cells will promote the natural regeneration of the nerve once implanted" (McFetridge ¶ 181; *see* Final Act. 5).

FF 6. McFetridge discloses that a "key component of . . . [peripheral nerve regeneration] process is the choice of 3D scaffold with which tissue growth

is guided," wherein "human umbilical artery (HUA) . . . because of its vascular derivation, it presents surfaces that are conducive to cellular attachment and subsequent [remodeling] processes" is "an excellent tubular structure scaffold for peripheral nerve reconstruction" (McFetridge ¶¶ 182–183; *see* Final Act. 5–6).

FF 7. Examiner finds that McFetridge fails to disclose that "the cells added to the arterial tissue matrix are exogenous mesenchymal stem cells" (Final Act. 7).

FF 8. Siemionow discloses that "[w]hen direct repair of the injured nerve with epineural sutures is impossible, the defect between the nerve stumps has to be bridged by a conduit of some kind, which will facilitate axonal regeneration towards the distal nerve stump" (Siemionow 1:9–12; *see* Final Act. 7).

FF 9. Siemionow discloses a "conduit material that causes minimal inflammatory reaction, and can serve as a structural guide for regenerating, or as a shield for protecting, nerve tissue (*e.g.*, axons)" and "methods of treating an injury to a (one or more) nerve or protecting a nerve in an individual in need thereof," wherein "[t]he methods employ all or a portion of an isolated, naturally occurring epineural sheath, and can be used, for example, to regenerate nerve tissue in an individual in need thereof" (Siemionow 2:29–3:4; *see id*. at 18:32–19:2 (Siemionow discloses methods that "comprise contacting the epineural sheath (*e.g.*, filling the graft; coating the sheath) with cells that aid and/or enhance regeneration of neural tissue."); *id.* at 19: 5–6 (Siemionow discloses that the seeded "cells can be autologous, allogenic, isogenic, xenogenic or a combination thereof (*e.g.*, chimeric cells.)"); *see generally id*. at 11:12–26; Final Act. 7).

FF 10. Siemionow discloses that its "epineural sheath can be filled with different types of cells including[, *inter alia*,] . . . mesenchymal stem cells" (Siemionow 21:16–18; *see* Final Act. 7).

FF 11. Examiner finds that although the combination of McFetridge, Siemionow, and Hadler suggest the use of an "arterial tissue matrix . . . derived from a pig," the combination fails to disclose a pig derived arterial tissue matrix that has been "genetically modified to have reduced expression of α-1,3-galactose," "lacks expression of α-galactosyltransferase," or "treated to remove α-1,3-galactose moieties" and relies on Ayares to make up for these deficiencies in the combination of McFetridge, Siemionow, and Hadler (Final Act. 7).

ANALYSIS

Based on the combination of McFetridge, Siemionow, Hadler, and Ayares, Examiner concludes, *inter alia*, that, at the time Appellant's invention was made, it would have been prima facie obvious to a person of ordinary skill in this art to combine: (1) McFetridge's disclosure of an implantable intact decellularized arterial tissue matrix, for treating a nerve, that is in the shape of a conduit and seeded with exogenous cells with (2) Siemionow's disclosure of a method of treating a nerve injury in an individual with a conduit material filled with exogenous mesenchymal stem cells to regenerate nerve tissue (*see* Final Act. 9; *see also* FF 1–10). We find no error in Examiner's prima facie case of obviousness.

As Examiner explains, the recitation of the phrases "for treating a nerve" and "wherein the exogenous mesenchymal stem cells added to the arterial tissue matrix improve repair, regrowth, and regeneration of nerve and muscle tissue compared to arterial tissue matrix alone when the arterial

tissue matrix is implanted across a defect in a nerve," as set forth in Appellant's claim 17, are intended use limitations (*see* Final Act. 4–5). "[T]he patentability of apparatus or composition claims depends on the claimed structure, not on the use or purpose of that structure." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002). *See Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1468 (Fed. Cir. 1990) ("[A]pparatus claims cover what a device *is*, not what a device *does*.").

We acknowledge Appellant's contention that "Examiner fails to make the required factual determination of the level of skill in the art" (Appeal Br. 6–7 (emphasis omitted)). Appellant's contention, however, is not persuasive because the prior art relied upon by Examiner is representative of the level of ordinary skill in this art (*see* Ans.[6] 6 (Examiner explains that the prior art relied upon is representative of the level of ordinary skill in this art)). *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("[T]he absence of specific findings on the level of skill in the art does not give rise to reversible error 'where the prior art itself reflects an appropriate level and a need for testimony is not shown.'" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

McFetridge discloses an implantable device that can be used for nerve regeneration comprising a substantially decellularized umbilical vessel, seeded with at least one cell type, such as *stem cells* (*see* FF 1–5). Siemionow discloses an implantable device that can be used for nerve regeneration comprising an epineural sheath seeded with cells that aid and/or

[6] Examiner's June 13, 2019 Answer.

enhance regeneration of neural tissue, such as exogenous *mesenchymal stem cells* (*see* FF 8–10). Thus, a person of ordinary skill in this art, reading McFetridge and Siemionow in combination, would have: (a) been motivated, and (b) found it prima facie obvious, to use Siemionow's mesenchymal stem cells, which aid and/or enhance regeneration of neural tissue, as the stem cells of McFetridge's device (*see e.g.,* Final Act. 9; *see also* Ans. 10 (Examiner explains that "[t]he simple substitution of the stem cells of McFetridge for the mesenchymal stem cells of Siemionow is nothing more than the simple substitution of one known element for another to obtain predictable results."); Ans. 15 (Examiner explains that a "skilled artisan would have found it *prima facie* obvious to substitute the generic stem cells of McFetridge for the mesenchymal stem cells [of] Siemionow because . . . Siemionow teaches mesenchymal stem cells . . . aid or enhance the regeneration of nerve tissue.") (quotation omitted)). *See In re Omeprazole Patent Litigation*, 483 F.3d 1364, 1374 (Fed. Cir. 2007) ("[T]his court finds no . . . error in [the] conclusion that it would have been obvious to one skilled in the art to substitute one ARC [alkaline reactive compound] for another."). Therefore, we are not persuaded by Appellant's contention that "Examiner offers no motivation or rationale to combine the teachings of McFetridge and Siemionow" (Appeal Br. 8 (citing Final Action 8–9); *cf.* Ans. 9–10). For the same reasons, we are not persuaded by Appellant's contention that Examiner's "[m]otivation to combine McFetridge and Siemionow could only arise through impermissible hindsight" (Appeal Br. 13).

For the foregoing reasons, we find that the prior art relied upon by Examiner provides a person of ordinary skill in this art with a reasonable

expectation of success in combining a decellularized umbilical vessel with exogenous mesenchymal stem cells into an implantable device (*see* FF 1–10; *see* Final Act. 10). Therefore, we are not persuaded by Appellant's contention that Examiner failed to establish a reasonable expectation of success on this record (*see* Appeal Br. 9–12; *see also* Reply Br. 3–4; *cf.* Ans. 9–10).

For the foregoing reasons, we are not persuaded by Appellant's contention that Examiner suggests the combination of "mesenchymal stem cell-filled epineural tube (decellularized conduit) of Siemionow with the stem-cell-seeded umbilical vessel of McFetridge to facilitate peripheral nerve regeneration" (Appeal Br. 13). As Appellant recognizes, such an interpretation of Examiner's prior art rejection "makes no sense" (*id.*).

> The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.

In re Keller, 642 F.2d 413, 425 (CCPA 1981).

We are not persuaded by Appellant's reliance on Keilhoff to support an assertion that Appellant's claimed product exhibits unexpected results (*see* Appeal Br. 5, 7, 8, 10–11 (citing Keilhoff,[7] 110–112 ; Spec. ¶¶ 20, 21, 69, 71, 73, 80–82 and FIG. 3); Reply Br. 3–4; *see also* Reply Br.[8] 3 (Appellant contends that "Examiner does not give proper weight to Keilhoof

[7] Keilhoff et al., *Mesenchymal stem cells for peripheral nerve regeneration–A real hope of just an empty promise?*, 232 Experimental Neurology 110–113 (2011).
[8] Appellant's August 12, 2019 Reply Brief.

in determining . . . the level of ordinary skill in the pertinent art."). In order to be persuasive of non-obviousness, "[e]vidence of secondary considerations must be reasonably commensurate with the scope of the claims." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). In addition, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter-Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

Keilhoff addresses why a particular document was "accepted for publication in Experimental Neurology" (Keilhoff 110). Specifically, Keilhoff discloses:

> Ladak et al. (2011) report on mesenchymal stem cells (MSCs), isolated from rat bone marrow, which were stimulated towards Schwann cell differentiation and then used to support peripheral nerve regeneration in vitro and in vivo. Such a paradigm is an interesting but not entirely new approach. . . . Nevertheless, the study of Ladak and co-workers has been accepted for publication in Experimental Neurology. Why?

(*Id.*) Keilhoff discloses that "Ladak and colleagues have consecutively evaluated the efficiency of MSCs in supporting axonal regeneration in vivo using a clinically available collagen nerve guide (Neurogen)" (*id.* at 111). Keilhoff recognizes, however, that "[a]lthough . . . [Ladak's] experimental design is well conducted, a comparison of stem cell seeded guides[, i.e. tubes,] with autografts is not quite accurate," because, *inter alia*, "the tube is different from the autograft" and "focus . . . [must be] on the physical properties of the scaffold, i.e. the extracellular matrix" (*id.*).

Appellant fails to identify an evidentiary basis on this record to support a conclusion that Keilhoff's Neurogen, a collagen tube, is "similar to the decellularized umbilizal vessel-based device of McFetridge," "the

epineural tube of Siemionow," or Appellant's arterial tissue matrix (Appeal Br. 10; *see also id*. at 16). "Attorney's argument in a brief cannot take the place of evidence." *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). Thus, Appellant fails to establish an evidentiary basis on this record to support a finding that Keilhoff discusses an implantable device that is both commensurate in scope with Appellant's claimed invention and provides a comparison with the closest prior art.

Appellant's contention regarding "a long felt but unsolved need," was presented for the first time in Appellant's Reply Brief (Reply Br. 4) and, therefore, was not properly presented to this panel for review. *See Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) (Appellant fails to "explain what 'good cause' there might be to consider the new argument. On this record, Appellant's new argument is belated.").

CONCLUSION

The preponderance of evidence relied upon by Examiner supports a conclusion of obviousness. The rejection of claim 17 under 35 U.S.C. § 103(a) as unpatentable over the combination of McFetridge, Siemionow, Hadler, and Ayares is affirmed. Claims 18–21, 25, 26, and 28–37 are not separately argued and fall with claim 17.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
17–21, 25, 26, 28–37	103	McFetridge, Siemionow, Hadler, Ayares	17–21, 25, 26, 28–37	

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