

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TISSUE TRANSPLANT TECHNOLOGY LTD. &
HUMAN BIOLOGICS OF TEXAS, LTD.,
Petitioner,

v.

MIMEDX GROUP, INC.,
Patent Owner.

Case IPR2015-00320
Patent 8,709,494 B2

Before LORA M. GREEN, SUSAN L. C. MITCHELL, and
CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Tissue Transplant Technology LTD (d/b/a Bone Bank Allografts) and Human Biologics of Texas, Ltd. (collectively, “Petitioner”) filed a corrected Petition requesting an *inter partes* review of claims 1–10 of U.S. Patent No. 8,709,494 B2 (Ex. 1001, “the ’494 patent”). Paper 7 (“Pet.”). MiMedx

Group, Inc. (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 11 (“Prelim. Resp.”).

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Upon considering the Petition and the Preliminary Response, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–10. Accordingly, we decline to institute an *inter partes* review of those claims.

A. *Related Proceedings*

Petitioner states that the ’494 patent is the subject of the copending district court case, *MiMedx Group, Inc. v. Tissue Transplant Technology Ltd. et al.*, Case No. 1:14-CV-719-HLH (W. D. Tex.). Pet. 1; Paper 9.

Petitioner also filed the following petitions against Patent Owner in the following requests for *inter partes* review: IPR2015-00420 (U.S. Patent No. 8,597,687 B2); IPR2015-00664 (U.S. Patent No. 8,372,437 B2); and IPR2015-00669 (U.S. Patent No. 8,323,701 B1).

B. *The ’494 Patent (Ex. 1001)*

The ’494 patent issued on April 29, 2014, with John Daniel listed as the sole inventor. Ex. 1001. The ’494 patent relates to tissue allografts, and more particularly “to placental membrane tissue grafts (amnion and chorion) and methods of preparing, preserving, and medical uses for the same.” *Id.* at 1:20–22.

As taught by the ’494 patent:

The placenta has two primary layers of tissue including amniotic membrane and chorion. The amniotic membrane is a

non-vascular tissue that is the innermost layer of the placenta, and consists of a single layer, which is attached to a basement membrane. Histological evaluation indicates that the membrane layers of the amniotic membrane consist of epithelium cells, thin reticular fibers (basement membrane), a thick compact layer, and fibroblast layer. The fibrous layer of amnion (i.e., the basement membrane) contains cell anchoring collagen types IV, V, and VII. The chorion is also considered as part of the fetal membrane; however, the amniotic layer and chorion layer are separate and separable entities.

Id. at 1:36–48. Placental membrane has been used for various types of reconstructive surgery since the early 1900s, and has also been widely used in ophthalmic procedures. *Id.* at 1:26–32.

According to the '494 patent, in order to prepare the implant, placental tissue is collected from a hospital. *Id.* at 5:7–8. The placenta is removed from the sterile shipment bag and transferred to a sterile processing basin preferably containing hyperisotonic saline (18% NaCl) solution at close to room temperature. *Id.* at 6:12–16. The placenta is gently massaged to help separate blood clots, allowed to reach room temperature to ease the separation of the amnion from the chorion, and then placed on a processing tray with the amniotic membrane layer facing down. *Id.* at 6:16–24.

With the tissues in the processing tray, the chorion layer is lifted gently off the amniotic membrane layer, and blood clots are removed from the layers using a blunt instrument, a finger, or a sterile, non-particulating gauze. *Id.* at 6:41–64. The tissue is chemically decontaminated, and then dehydrated on a drying fixture. *Id.* at 7:11–8:18. The drying fixture may have grooves, which may be arranged in a grid, and may also have a design in the empty spaces of the grid, such as a logo or name. *Id.* at 8:13–31. According to the '494 patent, “[p]referably, such texture/label can be read or viewed on the tissue in only one orientation so that, after drying and cutting,

an end user (typically a surgeon) of the dried tissue will be able to tell the stromal side from the basement side of the dried tissue.” *Id.* at 8:37–41. The drying fixture is placed in a dehydration bag, sealed, and placed in a frying oven at 35 to 50 degrees Celsius for 30 to 120 minutes. *Id.* at 8:58–9:15. The ideal drying conditions, however, appear to be at 45 degrees Celsius for 45 minutes. *Id.* at 9:5–8. Once the tissue is dehydrated, it can be cut into specific product sizes, and each cut allograft is placed into its own pouch. *Id.* at 9:22–23; 9:45–46.

C. Illustrative Claim

Petitioner challenges claims 1–10 of the ’494 patent, of which claims 1, 6, 9, and 10 are independent. Claim 1, 9, and 10 are illustrative and are reproduced below.

1. A dehydrated, laminated tissue graft consisting essentially of one or more washed and/or substantially cleaned amnion layers and one or more washed and/or substantially cleaned chorion layers, wherein at least one of the amnion layers contains its fibroblast cell layer, and further wherein the amnion layer and the chorion layer are directly laminated to each other.
9. A dehydrated, laminated, placental tissue graft which is a laminate comprising two or more separated and washed layers which layers are selected from amnion and/or chorion wherein the layers are directly laminated to each other and at least one of said layers is an amnion layer which retains an epithelial cell layer.
10. A dehydrated, laminated, placental tissue graft which is a laminate comprising two or more separated and washed layers which layers are selected from amnion and/or chorion wherein the layers are directly laminated to each other and at least one of said layers is an amnion layer which retains a fibroblast cellular layer.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–10 of the '494 patent on the following grounds:

References	Basis	Claims Challenged
Vishwakarma ¹	§ 102(b)/103(a)	9 and 10
Gray ²	§ 103(a)	1–10
Gray and Vishwakarma	§ 103(a)	1–10
Tseng ³ and Miljudin ⁴	§ 103(a)	9 and 10
Hariri ⁵ and Vishwakarma	§ 103(a)	1–10
Gray and Miljudin or Tseng	§ 103(a)	3, 9, and 10

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable constructions in light of the specification of the patent in which they appear. *See* 37 C.F.R. §42.100(b); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1280 (Fed. Cir.

¹ G. K. Vishwakarma and A. K. Khare (“Vishwakarma”), *Amniotic Arthroplasty for Tuberculosis of the Hip*, 68 J. BONE AND JOINT SURGERY 68–74 (1986) (Ex. 1005).

² Saleh M. Shenaq and Kathy Jo Gray (“Gray”), Pub. No. WO 93/10722, published Jun. 10, 1993 (Ex. 1006).

³ Tseng, US Patent No. 6,152,142, issued Nov. 28, 2000 (Ex. 1008).

⁴ Miljudin et al. (“Miljudin”), *Silica Gel Dissication of Amniotic Membrane with Related Epithelium Cells for Ocular Surface Reconstruction*, 5 CELL AND TISSUE BANKING 271–75 (2004) (Ex. 1007).

⁵ Hariri et al. (“Hariri”), Pub. No. US 2004/0048796 A1, published Mar. 11, 2004 (Ex. 1009).

2015). Under the broadest reasonable construction standard, claim terms are presumed to be given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). An inventor may rebut that presumption by providing a definition of the term in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

i. “*laminate*” or “*laminated*”

Petitioner argues that the Specification of the ’494 patent does not define the term “laminate” or “laminated.” Pet. 13. Petitioner does note that the Specification of the ’494 patent teaches that multiple layers are placed on the same drying fixture to create a laminate-type allograft material. *Id.* at 14 (citing Ex. 1001, 3:33–39). According to Petitioner, however, a person of ordinary skill in the art would understand the verb “laminate” to mean layering or uniting two layers, while the noun form would be understood as referring to the resulting product. *Id.* at 13–14 (citing Ex. 1002 ¶ 37; Ex. 1014).

Patent Owner responds that laminate should be construed as “separated and washed amnion and/or chorion layers that are *adhered* together.” Prelim. Resp. 7. Patent Owner argues that the Specification of the ’494 patent “expressly provides that the laminate is produced by adhering two or more amnion and/or chorion layers on top of one another to laminate the layers and thus create a single-unit multi-layer tissue graft.”

Id. at 7–8 (citing Ex. 1001, 2:7–9, 2:45–55, 3:33–39, and 8:51–57).

According to Patent Owner, layers that do not adhere to one another would not be able to form such a graft. *Id.* at 8. Finally, Patent Owner also points to the claim language of claim 9, which recites “a laminate,” that is, Patent Owner asserts, a single unit. *Id.* at 7.

For purposes of this Decision, we agree with Patent Owner, that consistent with the Specification of the ’494, “laminate” or “laminated” should be construed as requiring that the amnion and/or chorion layers be adhered together. In particular, as taught by the ’494 patent, the resulting dried laminate is cut and the resulting allograft is sealed in a pouch. Ex. 1001, 9:22–23, 9:45–46. Petitioner does not explain how chorion and/or amnion membranes that simply are layered on top of each other, but not adhered together, would result in a cohesive product that can be cut to form the tissue allograft.

ii. *All Remaining Terms*

We determine that, for purposes of this Decision, none of the other terms in the challenged claims requires express construction at this time.

B. *Principles of Law*

In order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). We must analyze prior art references as a skilled artisan would. *See Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991) (stating that to anticipate, “[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention”), *overruled on other grounds by*

Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282 (Fed. Cir. 2009). “Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.” *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981) (emphasis added) (citation omitted).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). An invention “composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. Moreover, a determination of unpatentability on the ground of obviousness must include “articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The obviousness analysis “should be made explicit” and it “can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR*, 550 U.S. at 418.

C. Anticipation/Obviousness over Vishwakarma (Ex. 1005)

Petitioner asserts that claims 9 and 10 are unpatentable as being anticipated, or rendered obvious, by Vishwakarma. Pet. 16–21.

i. Overview of Vishwakarma

Vishwakarma is drawn using an interposed, multi-layered cap of amniotic membrane in arthroplasty of the hip. Ex. 1005, Abstract.

Vishwakarma teaches a method for preparing the amniotic cap. *Id.* at 69. Specifically, Vishwakarma teaches:

The amniotic cap was prepared according to a technique which has been standardized at this centre. Fresh placentae were collected from the maternity centre and washed in running tap water for 10 minutes. Amnion was separated from the chorion, and amnion membrane, denuded of mucus, was collected in a beaker containing normal saline. Layers were then cut into squares and piled on a glass mould the size of a femoral head. There were 50 to 60 layers in each cap, the mesenchymal surface of the membrane always facing the glass mould. The amniotic cap was dried at ambient temperature for six to eight hours and a purse-string suture was then applied The dried cap was sterilized in 1% β -propiolactone for two hours before operation

Id. (citation omitted).

ii. Analysis

Petitioner asserts that claims 9 and 10 are unpatentable as being anticipated, or rendered obvious, by Vishwakarma. Pet. 16–21. As support, Petitioner relies on the Declaration of Dr. Daniel L. Mooradian (Ex. 1002), as well as the Declaration of Dr. James W. Poser (Ex. 1017). Patent Owner disagrees, relying on the deposition transcript of Dr. Mooradian (Ex. 2012). Prelim. Resp. 26–34.

As to the requirement of claims 9 and 10 that the layers be “directly laminated to each other,” Petitioner states that after separation of the

placental tissue, “the amnion is collected or submerged in saline and then laminated.” Pet. 17 (citing Ex. 1005, 69). Petitioner points also to the teaching in Vishwakarma that the amniotic cap was dried at ambient temperature for six to eight hours. *Id.* at 19 (claim chart).

Patent Owner argues that Vishwakarma does not disclose laminated amnion layers. Prelim. Resp. 32. In particular, Patent Owner contends the ordinary artisan, reading Vishwakarma, “would have understood that the squares of amniotic membrane are simply ‘piled’ on the glass mold but are *not* directly adhered to each other.” *Id.* at 32–33. In support, Patent Owner points to the teaching of Vishwakarma that a purse string suture is applied to hold the layers together, which would not be required if the layers had adhered together. *Id.* at 33.

As discussed above, Vishwakarma teaches layering 50 to 60 squares of amnion on a glass mold the size of a femoral head, which was then dried at ambient temperature. Ex. 1005, 69. A purse string suture was then applied. *Id.* at 69, Figure 1. Although it is possible that the amniotic layers of Vishwakarma may have adhered to one another through cellular or tissue interactions between the layers, inherency may not be established by mere possibilities. Except for the disclosure that the 50 to 60 squares were layered on a glass head and then dried, Petitioner points to no evidence, nor provides any scientific reasoning, demonstrating that the layers of amnion necessarily adhered to each other in the technique employed by Vishwakarma. Thus, Petitioner has not demonstrated a reasonable likelihood that Vishwakarma anticipates claims 9 and 10 of the ’494 patent.

As to the obviousness challenge, Petitioner asserts that it would have been obvious to the ordinary artisan “that Vishwakarma retains the epithelial

and fibroblast cell layers because Vishwakarma does not teach any methods to remove those layers.” Pet. 20–21. Petitioner does not address, however, why it would have been obvious to adhere the amnion layers of Vishwakarma to produce a laminate.

iii. Conclusion

For the reasons set forth above, Petitioner has not established a reasonable likelihood that claims 9 and 10 are anticipated, or rendered obvious, by Vishwakarma.

D. Obviousness over Gray (Ex. 1006)

Petitioner contends that claims 1–10 are unpatentable as obvious over Gray. Pet. 21–31.

i. Overview of Gray

Gray is drawn to “fetal membrane tubes for nerve and vessel grafts.” Ex. 1006, 1:6–7. As taught by Gray, the grafts are prepared by obtaining amnion and chorion from fresh placentas. *Id.* at 4:23–24. According to Gray:

the amnion and chorion layers are separated from the placenta and each other, cellular monolayer material overlying the basal lamina on the fetal side of the membrane is removed, such as by exposure to trypsin or pepsin, the amnion and chorion is rinsed repeatedly with phosphate buffer solution-or distilled water until clean, the amnion or chorion is then cross-linked either by exposure to gamma radiation or chemical cross-linking such as with glutaraldehyde, which sterilizes the tissue, provides protection against viral disease transmission, strengthens and permits remodeling the material from sheet to conduit form. The amnion and chorion sheets are then wrapped in layers so that the fetal surface, which is shiny, is directed toward the inner surface of the finished tube. The number of wraps will depend upon the length and diameter of the tube. The tubes are then dried and placed in bottles which are sealed, labeled and, if

desired, exposed to 2.5 M rads of gamma radiation to again sterilize and further cross-link the conduit collagen. If desired, the layers can be glued together by a suitable glue, such as a fibrin glue, to prevent delaminating, particularly in larger conduits, such as used for vascular grafts.

Id. at 4:25–5:9.

Gray teaches that it is also an object of the invention to provide a graft that comprises a cylindrical wall formed by sheets of sterilized collagen, Types I, II, and III, derived from human placenta from which the cellular material has been substantially removed. *Id.* at 5:23–29.

ii. Analysis

Petitioner asserts that claims 1–10 are unpatentable as being rendered obvious by Gray. Pet. 21–31. As support, Petitioner relies on the Declaration of Dr. Mooradian (Ex. 1002). Patent Owner disagrees. Prelim. Resp. 35–42.

Specifically, as to the issue of whether the grafts of Gray retain a fibroblast or epithelial cell layer, Petitioner contends that while Gray teaches the use of trypsin to remove the epithelial cellular layer, the ordinary artisan would understand that treatment with trypsin “would be ineffective for removing fibroblasts embedded in a three-dimensional extracellular such as the fibroblast layer or spongy layer.” Pet. 22 (citing Ex. 1002 ¶ 60). In addition, Petitioner cites claims 1 and 2 of Gray as representing an embodiment in which “Gray teaches that cell layers are not removed.” *Id.* at 23.

Petitioner contends further that the ordinary artisan would understand that “Gray specifically teaches the removal of the epithelial layer to promote axon growth and not for anything related to the lamination or dehydration processing steps.” *Id.* at 22–23 (citing Ex. 1002 ¶ 61). In particular,

Petitioner argues that the ordinary artisan would understand that “Gray’s disclosure of removing the epithelial layer as important for nerve grafts but not necessary or important for blood vessel grafts.” *Id.* at 24 (citing Ex. 1002 ¶ 60).

Petitioner concludes, therefore, that the ordinary artisan would understand that not all applications of placental tissue grafts would require exposure of the basement membrane, and would be motivated to modify the method of Gray to allow for retention of the epithelial cell layer, which would simplify and shorten processing of the graft. *Id.* at 24–25 (citing Ex. 1002 ¶¶ 61–62).

Patent Owner responds that because Gray teaches that “the collagen tubes of the invention are processed such that ‘**cellular material is substantially removed**,’ one of ordinary skill in the art reading Gray would have understood that the goal of the invention was *decellularization* of the amniotic and chorionic membranes.” Prelim. Resp. 35 (citing Ex. 1006, 5:23–35, 12:23–35). In particular, Patent Owner argues that Petitioner only provides an unsupported assertion that the methods of Gray would not remove the fibroblast cells or the fibroblast cell layer, but no evidence in support of that assertion. *Id.* at 36. Moreover, Patent Owner contends that the only motivation to modify Gray provided by Petitioner is to simplify the processing, but Gray provides a specific reason to decellularize the layers, which is to reduce immunogenicity. *Id.* at 37–38.

We agree with Patent Owner that Petitioner has not established a reasonable likelihood that claims 1–10 are rendered obvious by Gray. Notably, we agree with Patent Owner that Gray teaches a graft comprising sheets of sterilized collagen, Types I, II, and III, derived from human

placenta, and from which the cellular material has been substantially removed. Ex. 1006, 5:23–29.

We have considered the disclosure of claims 1 and 2 of Gray, as well as the Declaration of Dr. Mooradian, but they do not convince us otherwise. The claims of Gray must be read in light of the disclosure, and Petitioner does not point us to any teaching, nor to any claim, that specifies that the fibroblast cell layer is retained in the placental graft of Gray. Nor does Petitioner point us to any additional decellularization step in Gray that is used to remove the fibroblast cell layer.

Petitioner relies on the Declaration of Dr. Mooradian to support its assertion that the use of trypsin or pepsin will not remove the fibroblast cell layer. Pet. 22. Dr. Mooradian, however, merely provides the conclusory statement that the ordinary artisan would understand that trypsin acts by disrupting the attachment of cells to the extracellular matrix, and thus, while trypsin may be used to remove epithelial cells, “it would be ineffective for the purpose of removing fibroblasts embedded in a three-dimensional matrix such as would be found in the fibroblast layer or spongy layers of the amnion.” Ex. 1002 ¶ 60. Dr. Mooradian does not provide any evidence to support that statement, and that statement is, thus, entitled to little weight. 37 C.F.R. § 42.65(a). Moreover, Dr. Mooradian does not address the statement in Gray that the graft comprises sheets of sterilized collagen, Types I, II, and III, derived from human placenta from which the cellular material has been substantially removed. Ex. 1006, 5:23–29.

iii. Conclusion

For the reasons set forth above, Petitioner has not established a reasonable likelihood that claims 1–10 are rendered obvious by Gray.

*E. Obviousness over the Combination of Gray (Ex. 1006)
and Vishwakarma (Ex. 1005)*

Petitioner contends that claims 1–10 are unpatentable as obvious over Gray and Vishwakarma. Pet. 31–36. As support, Petitioner relies on the Declaration of Dr. Mooradian (Ex. 1002). Patent Owner disagrees. Prelim. Resp. 42–47.

The disclosures of Gray and Vishwakarma are discussed above. According to Petitioner, “Vishwakarma discloses a simplified method of placenta processing resulting in a dehydrated, non-decelled laminate comprised of amnion,” and “Gray teaches a more complex method of processing that includes additional washing, treatment to reduce infection potential, and partial decellularization that results in a dehydrated laminate comprised of amnion and/or chorion.” Pet. 31.

Petitioner contends that the ordinary artisan would understand that the removal of cells, such as the epithelial cellular layer, is not required in preparing placental cell grafts unless there is a need to do so. *Id.* (citing Ex. 1002 ¶ 65). Petitioner relies on Vishwakarma for teaching that both lamination and dehydration are viable with amnion that has not been decellularized, arguing that it would have been obvious “to include the more substantial washing steps and treatment with a sterilant of Gray into the processing of Vishwakarma to reduce infection potential without impacting the capability of the non-decelled tissue to be laminated or dehydrated.” *Id.* at 31–32.

Patent Owner responds that Petitioner has not provided a reason to combine Gray with Vishwakarma, as the invention of Gray is premised on the decellularization of the amniotic and/or chorionic membranes. Prelim. Resp. 43. Instead, according to Patent Owner, Petitioner and its declarant

state, without relying on any supporting evidence, that it would be obvious to eliminate the decellularization step. *Id.*

We agree with Patent Owner that Petitioner has not demonstrated a reasonable likelihood that the combination of Gray and Vishwakarma renders claims 1–10 obvious. Petitioner relies on Vishwakarma as demonstrating that lamination and dehydration are viable with amnion that has not been decellularized. Pet. 31. As discussed above as to the challenge of claims 9 and 10 as being anticipated or rendered obvious by Vishwakarma, however, Petitioner has not demonstrated that Vishwakarma provides a laminate in which the layers are adhered together. Moreover, while Gray does teach a laminate, Petitioner and Dr. Mooradian only provide a conclusory statement, without any articulated reasoning, that it would have been obvious to retain the cells on the graft of Gray. “[O]bviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *Kahn*, 441 F.3d at 988.

iii. Conclusion

For the reasons set forth above, Petitioner has not established a reasonable likelihood that claims 1–10 are rendered obvious by the combination of Gray and Vishwakarma.

F. Obviousness over the Combination of Tseng (Ex. 1008) and Miljudin (Ex. 1007)

Petitioner contends that claims 9 and 10 are unpatentable as obvious over Tseng and Miljudin. Pet. 36–41.

i. Overview of Tseng (Ex. 1008)

Tseng is drawn to “amniotic membrane grafts especially usable in the repair of injured eyes.” Ex. 1008, 1:14–15. In preparing the graft, placenta is rinsed with balanced saline, which preferably contains antibiotics, to remove excessive blood clots. *Id.* at 4:60–65. While immersed in the solution, the amnion is separated from the chorion by blunt dissection. *Id.* at 5:7–10. The separated amniotic sheet is then mounted on a substrate, such as a sterile nitrocellulose paper, such that the epithelial surface is kept facing up, and the stromal/fibroblastic surface is layered on the substrate. *Id.* at 5:10–14. According to Tseng, when used as a surgical graft to treat ulceration of the eye, the amniotic membrane is peeled off the substrate. *Id.* at 6:16–31. Tseng teaches further that one layer is generally sufficient, but that “it is also feasible to use two or more layers.” *Id.* at 6:38–39.

ii. Overview of Miljudin (Ex. 1007)

Miljudin looked at the properties of amniotic membrane treated with antibiotics, dried over silica gel, and then sterilized by gamma rays. Ex. 1009, Abstract. Specifically, placentas are collected, and amnion is separated from chorion that has been washed free of blood clots. *Id.* at 272. The amniotic membrane is treated with glycerol, and fixed on frames over silica gel for 18 to 24 hours, and then sterilized by gamma rays. *Id.* at 272–273. The amniotic membrane still has epithelial cells, although there is a decrease in their number, and they have lost their “vital capacity.” *Id.* at 273.

ii. Analysis

Petitioner asserts that claims 9 and 10 are unpatentable as obvious over Tseng and Miljudin. Pet. 36–41. As support, Petitioner relies on the

Declaration of Dr. Mooradian (Ex. 1002). Patent Owner disagrees. Prelim. Resp. 47–51.

As to the requirement of a laminated, placental tissue graft, Petitioner relies on the teaching in Tseng that two or more layers of an amnion tissue graft may be used to fill deep ulcerations, and contends that the layering of multiple amnion membranes creates a laminate. Pet. 37 (relying on Ex. 1008, 6:18–39; Ex. 1002 ¶ 74); *see also id.* at 39 (claims chart pointing to support for laminate). Petitioner argues that it would have been obvious to use the dehydration and processing steps of Miljudin with the multi-layer laminate of Tseng, which would allow for the elimination of the need for nitrocellulose paper and freezer based storage. *Id.* at 39 (citing Ex. 1002 ¶ 76).

Patent Owner responds that Petitioner has not established that Tseng and Miljudin, either separately or combined, teach a placental tissue graft in which the layers are directly laminated to one another. Prelim. Resp. 47–48. According to Patent Owner, both Tseng and Miljudin are drawn to single layer grafts, and although the grafts of Tseng may be layered, Dr. Mooradian admits that the layers are not adhered to one another. *Id.* at 50–51 (citing Ex. 1002 ¶ 74).

We agree with Patent Owner that Petitioner has not demonstrated a reasonable likelihood that the combination of Tseng and Miljudin renders claims 9 and 10 obvious. Specifically, Petitioner relies on the teaching of Tseng that two or more layers of a placental graft may be layered to treat deep ulcerations. We have construed the term “laminated” as requiring the layers to be adhered together. Petitioner has provided no evidence or scientific reasoning as to how layering two or more placental grafts in a deep

ulceration would necessarily result in the layers adhering together to form a laminate. Nor has Petitioner provided evidence or scientific reasoning that it would have been obvious based on Tseng's and Miljudin's teachings to create a laminate by adhering the layers.

iii. Conclusion

For the reasons set forth above, Petitioner has not established a reasonable likelihood that claims 9 and 10 are rendered obvious by the combination of Tseng and Miljudin.

*G. Obviousness over the Combination of Hariri (Ex. 1009)
and Vishwakarma (Ex. 1005)*

Petitioner contends that claims 1–10 are unpatentable as obvious over Hariri and Vishwakarma. Pet. 41–53.

i. Overview of Hariri (Ex. 1009)

Hariri is drawn to a collagen biofabric produced from amnion. Ex. 1009 ¶ 2. The collagen biofabric is prepared by decellularizing the amniotic membrane, and preferably, the membrane is completely decellularized. *Id.*

In the method of Hariri, the amniotic membrane is separated from the chorionic membrane. *Id.* at ¶ 80. The membrane is then decellularized to remove substantially all of the cells normally associated with the collagen matrix, preferably by using a weak detergent solution. *Id.* at ¶¶ 83, 86. After additional washing steps to remove any cellular debris, the membrane is dried, preferably under vacuum. *Id.* at ¶¶ 93, 101.

Hariri also discloses the production of laminates. *Id.* at ¶ 113. The laminates may be prepared by layering the decellularized membrane, and then drying the layered membrane, or by layering the dried membrane. *Id.* at ¶¶ 115–116. Hariri also teaches the use of an adhesive or cross-linking to prepare the laminate. *Id.* at ¶ 117.

Hariri specifically compares the use of decellularized grafts with grafts that may have dead cells present, concluding that anecdotal evidence is suggestive that when dead cells are present, healing times are longer and rejection rates are higher. *Id.* at Table 1.

ii. Analysis

Petitioner asserts that claims 1–10 are unpatentable as being rendered obvious by the combination of Hariri and Vishwakarma. Pet. 41–53. As support, Petitioner relies on the Declaration of Dr. Mooradian (Ex. 1002). Patent Owner disagrees, relying on the deposition transcript of Dr. Mooradian (Ex. 2012). Prelim. Resp. 51–56.

An overview of Vishwakarma is presented above. Petitioner contends that Hariri alone renders obvious claims 1–10, as “[w]ithout a specific reason to decellularize,” the ordinary artisan would have eliminated that step of Hariri “to simplify processing and shorten the time required.” Pet. 44 (citing Ex. 1002 ¶ 86). In the alternative, Petitioner contends that it would have been obvious to a person of ordinary skill in the art to use non-decelled placental tissue as taught by Vishwakarma, with the lamination techniques and gross processing of Hariri, as Vishwakarma teaches lamination of at least two layers on non-decelled amnion tissue with subsequent drying, demonstrating that lamination is possible with non-decelled tissue. *Id.* at 44.

Patent Owner contends that the only reason provided by Petitioner to combine Vishwakarma with Hariri is to simplify processing by removing the decellularization step, which Petitioner characterizes as unnecessary. Prelim. Resp. 51–52. Patent Owner argues, however, that the decellularization step of Hariri, resulting in a collagen matrix that is devoid of cells, allows for the transportation of biomolecules or living cells. *Id.* at

52 (citing Ex. 1002 ¶ 86). In addition, Patent Owner argues that “Hariri also states that evidence suggests that even the presence of **dead** cells may have negative consequences, leading to a higher rejection rate and longer healing time.” *Id.* (citing Ex. 1009, Table 1).

We agree with Patent Owner that Petitioner has not demonstrated a reasonable likelihood that the combination of Hariri and Vishwakarma renders claims 1–10 of the ’494 patent obvious. As to Petitioner’s argument that it would have been obvious to not remove the cells layers in producing the placental graft of Hariri without a specific reason to do so, we find that to be a conclusory statement without sufficient support to conclude that Petitioner has demonstrated a reasonable likelihood of obviousness. *Kahn*, 441 F.3d at 988. Moreover, as noted by Patent Owner, Table I of Hariri provides reasons why decellularized grafts are advantageous over grafts in which dead cells may be present. And as acknowledged by Dr. Mooradian, Hariri teaches that the cells are removed so that the collagen matrix can transport biomolecules or living cells. Ex. 1002 ¶ 86.

As to the combination of Hariri with Vishwakarma, Petitioner has not demonstrated that Vishwakarma provides a laminate in which the layers are adhered together, and thus, does not demonstrate that lamination is possible with non-decelled tissue. Thus, Vishwakarma does not add anything to Hariri to support Petitioner’s contention of obviousness.

iii. Conclusion

For the reasons set forth above, Petitioner has not established a reasonable likelihood that claims 1–10 are rendered obvious by the combination of Hariri and Vishwakarma.

*H. Obviousness over the Combination of Gray (Ex. 1006)
and Miljudin (Ex. 1007) or Tseng (Ex. 1008)*

Petitioner contends that claims 3, 9, and 10 are unpatentable as obvious over Gray and Miljudin or Tseng. Pet. 53–58. As support, Petitioner relies on the Declaration of Dr. Mooradian (Ex. 1002). Patent Owner disagrees. Prelim. Resp. 56–58.

The disclosures of Gray, Miljudin, and Tseng are discussed above. Petitioner relies on Miljudin and/or Tseng for the teaching of the use of antibiotics to treat amnion prior to use, contending that it would have been obvious to the ordinary artisan to treat the separated amnion and chorion layers of Gray with antibiotics prior to lamination. Pet. 53 (citing Ex. 1002 ¶¶ 92–93. Petitioner does not explain, however, how either Miljudin or Tseng remedies the deficiencies of Gray as set forth in Section II(D) above.

iii. Conclusion

For the reasons set forth above, Petitioner has not established a reasonable likelihood that claims 3, 9, and 10 are rendered obvious by the combination of Gray and Tseng or Miljudin.

III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing any of claims 1–10 of the '494 patent are unpatentable under 35 U.S.C. § 102(b) or 35 U.S.C. § 103(a).

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied* as to all of the challenged claims of the '494 patent.

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Patent 8,709,494 B2

PETITIONER:

Robert McRae
Jason McKinnie
GUNN, LEE & CAVE, PC
rmcrae@gunn-lee.com
jmckinnie@gunn-lee.com

PATENT OWNER:

Keith E. Broyles
Thomas J. Parker
Christopher T. L. Douglas
ALSTON & BIRD LLP
Keith.Broyles@alston.com
Thomas.Parker@alston.com
Chris.Douglas@alston.com