UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MUSCULOSKELETAL TRANSPLANT FOUNDATION,
Petitioner,

v.

MIMEDX GROUP, INC.,
Patent Owner.

_____

Case IPR2015-00664
U.S. Patent No. 8,372,437 B2

_____

PATENT OWNER'S NOTICE OF APPEAL

Director of the United States Patent and Trademark Office
c/o Office of the General Counsel
Madison Building East, 10B20
600 Dulany Street
Alexandria, VA 22314-5793

Notice is hereby given, pursuant to 37 C.F.R. § 90.2(a), that Patent Owner MiMedx Group, Inc. ("MiMedx") appeals to the United States Court of Appeals for the Federal Circuit from the Final Written Decision entered by the Patent Trial and Appeal Board (the "Board") as Paper No. 49 on August 16, 2016 (the "Final Written Decision," a copy of which is attached hereto as Exhibit A).

In accordance with 37 C.F.R. § 90.2(a)(3)(ii), MiMedx further indicates that the issues on appeal may include, without limitation:

(i) Whether the Board erred in determining that Petitioner Musculoskeletal Transplant Foundation proved by a preponderance of the evidence that Claims 1-2 of U.S. Patent No. 8,372,437 B2 are unpatentable under 35 U.S.C. § 103(a), along with all reasons, findings, opinions, and orders leading to or underlying that determination including, without limitation, its determination that "washing and substantially cleaning" does not require removal of substantially all of the spongy layer; and

(ii) Whether the Board otherwise erroneously exercised or exceeded its authority.

Simultaneously with this submission, a copy of this Notice of Appeal is being filed with the Board and an electronic copy, along with the required docketing fee, are being filed with the United States Court of Appeals for the Federal Circuit.

Dated: October 11, 2016

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 90.2, the undersigned hereby certifies that, on October 11, 2016, a true copy of the foregoing Patent Owner's Notice of Appeal was delivered by hand to the Director of the United States Patent and Trademark Office, at the following address:

Director of the United States Patent and Trademark Office
c/o Office of the General Counsel
Madison Building East, 10B20
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The undersigned further certifies that, pursuant to 37 C.F.R. § 1.983, on October 11, 2016, an electronic copy of the foregoing Patent Owner's Notice of Appeal, along with the required docketing fee, was submitted electronically with the United States Court of Appeals for the Federal Circuit.

Furthermore, pursuant to 37 C.F.R. § 42.6(e), the undersigned hereby certifies that, on October 11, 2016, a true copy of the foregoing Patent Owner's Notice of Appeal was served upon the following via electronic delivery:

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Exhibit A

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Paper No. 49
Filed: August 16, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MUSCULOSKELETAL TRANSPLANT FOUNDATION,
Petitioner,

v.

MIMEDX GROUP, INC.,
Patent Owner.

Case IPR2015-00664
Patent 8,372,437 B2

Before LORA M. GREEN, CHRISTOPHER G. PAULRAJ, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Musculoskeletal Transplant Foundation ("Petitioner") filed a Corrected Petition requesting an *inter partes* review of claims 1 and 2 of U.S. Patent No. 8,372,437 B2 (Ex. 1001, "the '437 patent"). Paper 11 ("Pet."). MiMedx Group, Inc. ("Patent Owner") filed a Corrected Preliminary Response to the Petition. Paper 10 ("Prelim. Resp."). We determined that the information presented in the Petition and the Preliminary Response demonstrated that there was a reasonable likelihood that Petitioner would prevail in challenging claims 1 and 2 as unpatentable under 35 U.S.C. § 103(a). Pursuant to 35 U.S.C. § 314, the Board instituted trial on August 18, 2015, as to the challenged claims of the '437 patent. Paper 13 ("Institution Decision" or "Dec. Inst.").

Patent Owner filed a Response (Paper 27, "PO Resp."), but did not file a motion to amend. Petitioner subsequently filed a Reply. Paper 31 ("Reply"). An oral hearing was held on April 26, 2016, and a transcript of the hearing has been entered into the record (Paper 47). Patent Owner filed a Motion to Exclude (Paper 38), to which Patent Owner filed an Opposition (Paper 40), and Patent Owner filed a Reply (Paper 42).

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Based on the record before us, we conclude that Petitioner has demonstrated by a preponderance of the evidence that claims 1 and 2 of the '437 patent are unpatentable.

A. Related Proceedings

Petitioner states that the '437 patent is the subject of a copending district court case, *MiMedx Group, Inc. v. Liventa Bioscience Inc. et. al.*, Case No. 1:14-CV-01178-MHC (N.D. Ga.). Pet. 1; Paper 7, 1.

Petitioner also filed a petition for *inter partes* review of U.S. Patent No. 8,323,701 B2 against Patent Owner in IPR2015-00669, in which we denied institution. IPR2015-00669, Paper 13, 30.

B. The '437 Patent (Ex. 1001)

The '437 patent issued on February 12, 2013, with John Daniel listed as the sole inventor. Ex. 1001. The '437 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 1:15–17.

As taught by the '437 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 1:32–45. 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 1:22–28. The '437 patent teaches that

"[t]ypically, such membrane is either frozen or dried for preservation and storage until need for surgery." *Id.* at 1:28–30.

According to the '437 patent, in order to prepare the implant, placental tissue is collected from a hospital. *Id.* at 4:65–66. 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 5:65–6:2. 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 6:2–10.

With the placental tissue 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 6:27–62. In particular, the '437 patent teaches:

> Care is then taken to remove blood clots and other extraneous tissue from each layer of tissue until the amniotic membrane tissue and the chorion are clean and ready for further processing. More specifically, the amnion and chorion tissues are placed on the processing tray and *blood clots* are carefully removed using a blunt instrument, a finger, or a sterile non-particulating gauze, *by gently rubbing the blood until it is free from the stromal tissue of the amnion and from the trophoblast tissue of the chorion*. The stromal layer of the amnion is the side of the amniotic membrane that faces the mother. In contrast, the basement membrane layer is the side of the amnion that faces the baby.
>
> Using a blunt instrument, a cell scraper or sterile gauze, *any residual debris or contamination is also removed*. This step must be done with adequate care, again, so as not to tear the amnion or chorion tissues. The cleaning of the amnion is complete once the amnion tissue is smooth and opaque-white in appearance. If the amnion tissue is cleaned too much, the opaque

> layer can be removed. Any areas of the amnion cleaned too aggressively and appear clear will be unacceptable and will ultimately be discarded.

Id. at 6:42–62 (emphasis added).

The tissue is chemically decontaminated, and then dehydrated on a drying fixture. *Id.* at 6:63–8:64. 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 7:61–8:11. The drying fixture is placed in a dehydration bag, sealed, and placed into a drying oven at 35 to 50 degrees Celsius for 30 to 120 minutes. *Id.* at 8:38–8:61. The ideal drying conditions, however, appear to be at 45 degrees Celsius for 45 minutes. *Id.* at 8:51–55. 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 8:65–9:8; 9:22–29.

The ’437 patent states:

> Accordingly, while the present invention has been described herein in detail in relation to preferred embodiments, it is to be understood that this disclosure is only illustrative and exemplary of the present invention and is made merely for purposes of providing a full and enabling disclosure of the invention. The foregoing disclosure is not intended nor is to be construed to limit the present invention or otherwise to exclude any such other embodiments, adaptations, variations, modifications and equivalent arrangements, the present invention being limited only by the claims appended hereto and the equivalents thereof.

Id. at 10:59–11:3.

C. Illustrative Claim

Petitioner challenges claims 1 and 2 of the ’437 patent. Claim 1 is the only independent claim and is reproduced below:

> 1. A dehydrated, laminated tissue graft, wherein the tissue graft is produced by a process consisting of:
>
> isolating an intact amnion layer;
>
> isolating a chorion layer;
>
> washing and substantially cleaning the amnion layer and the chorion layer;
>
> laminating the amnion and chorion layer together; and
>
> dehydrating the laminated graft to produce the dehydrated, laminated tissue graft.

Ex. 1001, 11:6–12:6.

Dependent claim 2 specifies that the washing is carried out in an antibiotic solution. *Id*. at 12:7–8.

D. Instituted Challenges

We instituted trial based on the following grounds of unpatentability (Dec. Inst. 18):

References	**Basis**	**Claims Challenged**
Klen[1] and Sulner[2]	§ 103(a)	1
Klen, Sulner, and Tseng[3]	§ 103(a)	2

Petitioner relies on the Declaration of Helen N. Jones, Ph.D. Ex. 1010. Patent Owner relies on the Declaration of Rebecca N. Baergen, M.D. Ex. 2030.

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[1] R. KLEN, *Preparation of Chorion and Amnion Grafts Used in Burns*, RESEARCH IN BURNS 289–92 (P. Matter et al., 1971) (Ex. 1013).

[2] Sulner et al. ("Sulner"), Pub. No. US 2007/0038298 A1, published Feb. 15, 2007 (Ex. 1015).

[3] Tseng, US Patent No. 6,326,019 B1, issued Dec. 4, 2001 (Ex. 1011).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the Specification of the patent in which they appear. *See* 37 C.F.R. §42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–2145 (2016) (upholding the use of the broadest reasonable interpretation standard). Under the broadest reasonable construction standard, claim terms are presumed to have 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).

"[T]he specification 'is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term.'" *In re Abbott Diabetes Care Inc.*, 696 F.3d 1142, 1149 (Fed. Cir. 2012) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed.Cir.2005) (en banc)). The Court of Appeals for the Federal Circuit has cautioned, however, "[t]here is a fine line between construing the claims in light of the specification and improperly importing a limitation from the specification into the claims." *Retractable Techs., Inc. v. Becton, Dickinson, and Co.*, 653 F.3d 1296, 1305 (Fed. Cir. 2011). Thus, "[e]ven when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction.'" *Hill-Rom Services, Inc. v. Stryker Corp.*, 755 F.3d 1367, 1372 (Fed. Cir. 2014); *see also SuperGuideCorp. v. DirecTV*

Enterprises, Inc., 358 F.3d 870, 875, 69 USPQ2d 1865, 1868-69 (Fed. Cir. 2004) ("Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into the claim limitations that are not part of the claim. For example, a particular embodiment in the written description may not be read into a claim when the claim language is broader than the embodiment.");

i. "intact amnion"

Claim 1 is a product-by-process claim drawn to a tissue graft that is produced by the recited process. The patentability of a product-by-process claim does not depend on the specified method of production, but on the product itself. *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). Stated differently, "[i]f the product in a product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *Id.* If, however, the process by which a product is made imparts "structural and functional differences" from the product of the prior art, then those differences are relevant to the patentability analysis. *Greenliant Sys., Inc. v. Xicor*, 692 F.3d 1261, 1268 (Fed. Cir. 2012).

Claim 1 recites the term "intact amnion layer" in the process portion of the claim, that is, the step of "isolating an intact amnion layer." That intact amnion layer is then subject to washing and cleaning steps, a lamination step, as well as a dehydrating step. But as Patent Owner itself notes, "[a]mniotic membrane is a delicate tissue" (Prelim. Resp. 18), and, thus, the ordinary artisan would understand that the washing, cleaning, laminating, and drying steps would result in changes to the amnion, such

that the amnion could no longer be considered intact in the final product claimed by challenged claim 1.

For purposes of the Decision on Institution, we did not construe the claim as requiring that dehydrated, laminated tissue graft contain an intact amnion. Dec. Inst. 7. We concluded that the product-by-process of claim 1 required only that the dehydrated tissue graft that may be produced by a process in which intact amnion is subject to the washing, cleaning, laminating, and drying steps as set forth in challenged claim 1.

In its Response, Patent Owner argues that we erred in our construction, as claim 1 requires only a dehydrating step, not a freeze-drying step. PO Resp. 8. We acknowledge that while we referred to freeze-drying in the portion on claim construction (Dec. Inst. 7), in summarizing the teaching of the '437 patent, we explicitly observed that the disclosure teaches that the graft is preferably dehydrated on a drying fixture which is placed in a dehydration bag, sealed, and placed in a drying oven at 35 to 50 degrees Celsius for 30 to 120 minutes (*id.* at 4). Thus, our reference to "freeze-drying," rather than simply "dehydrating," was a typographical error. Moreover, although claim 1 does not require the use freeze-drying as the dehydration step, it does not exclude the use of freeze-drying as the dehydration step.

Patent Owner argues further that our construction "leaves unanswered the question of exactly *how* different the claimed amnion layer is" after undergoing the claimed steps. PO Resp. 8. Patent Owner contends that "the plain language of the claims and file history of the '437 Patent show that the amnion layer in the final product must, at a minimum, not have undergone substantial decellularization (*i.e.* removal of more than 90% of cells from the

amnion layer of the graft)." *Id.* at 8–9. Stated differently, Patent Owner proposes a construction in which the amnion layer may have only 10% of the cells of the amnion layer of the graft, and still be encompassed by the claim.

Patent Owner points to the language of the claims themselves, asserting that claim 1 uses the transition phrase "consisting of," but does not recite a decellularization step. *Id*. at 9. Patent Owner avers that, given this claim formulation, "the final graft *cannot* include a substantial decellularizing step." *Id.* According to Patent Owner, Petitioner's expert, Dr. Jones, agrees that the graft could not have undergone a substantial decellularization step, as Dr. Jones distinguishes the possible loss of a small number of cells during performance of the steps of the '437 patent from "the substantial decellularization of Sulner and Hariri." *Id.* at 9 n.1 (citing Ex. 2027, 259:20–263:21 ("a relatively small number of the cells could be removed" during a washing step), 265:4–269:5 (the number of cells lost is not quantifiable because it "could change with each — with each time you wash that tissue"); *see also id.* at 11 (citing Ex. 2027, 191:23–195:25 (some cells may be removed during the washing, cleaning, dehydrating, and/or laminating steps of the '437 patent); Ex. 2025 ¶¶ 131–133, 139, 142–143). In particular, Patent Owner notes that Dr. Jones testified that "the final, claimed graft of the '437 Patent has not undergone any treatment that would constitute substantial decellularization of the graft (*e.g.*, removal of 90% or more of the cells)." *Id.* at 11 (citing Ex. 2027, 191:23–195:25; Ex. 2025 ¶¶ 131–133, 139, 142–143).

Patent Owner argues further that the prosecution history supports its construction. *Id.* at 10. In particular, Patent Owner asserts that "the file

history explicitly distinguishes the claimed graft of the '437 Patent from prior art grafts (namely, Hariri) on the basis that the prior art grafts substantially decellularized the amnion layer (*i.e.* at least 90% of cells removed)." *Id.* (citing Ex. 1002, 38, 52; Ex. 2025 ¶¶ 131–132).

> Patent Owner quotes the Notice of Allowability, which states that
>
> [w]ith regards to the "washing and substantially cleaning" step, it is submitted that the specification makes it clear that this washing and cleaning only achieves removal of blood and the spongy/connective layer, not actual cellular layers of either of the amnion or chorion layers.

Id. at 11 (quoting Ex. 1002, 28–29; citing Ex. 2025 ¶ 104; Ex. 1010 ¶¶ 75, 161).

Petitioner responds that Patent Owner's "attempt to rewrite the claims to allow for ***up to 90% decellularization*** is . . . at odds with its representations to the Patent Office." Reply 7. Specifically, Petitioner contends that Patent Owner represented during prosecution that the claims did not include a decellularization step, and the "fact that the terms 'consisting of' and 'intact' were added to the claims to distinguish over the prior art's disclosure of more than 90% decellularized amnion does not entitle PO to claim a range of decellularization up to 90%." *Id.* at 7–8. Moreover, Petitioner asserts, the Specification does not provide any disclosure as to decellularization, much less any specific range relating to decellularization. *Id.* at 8.

Petitioner avers that we fully addressed Patent Owner's arguments in the Decision on Institution, where we stated that the claims were written as product-by-process claims, and that the claims only required that the amnion be intact at the beginning of the process. *Id.* In addition, we noted that as acknowledged by Patent Owner, amniotic tissue is delicate. *Id.* Thus,

Petitioner contends that the construction adopted in the Decision on Institution that the dehydrated tissue graft that is "produced by a process in which the intact amnion is subject to the washing, cleaning, laminating, and [dehydrating] steps as set forth in challenged claim 1" is correct. *Id.* at 9 (citing Dec. Inst. 7).

As we noted in our Decision on Institution (Dec. Inst. 6), and as we reiterate above, claim 1 is drawn to a product-by-process claim. Claim 1 does not specify the characteristics of the product, but requires only that it be produced by the steps of 1) isolating an intact amnion layer; 2) isolating a chorion layer; 3) washing and substantially cleaning the amnion layer and the chorion layer; 4) laminating the amnion layer and the chorion layer together; and 5) dehydrating the laminated graft to produce the dehydrated, laminated tissue graft.

As noted by Petitioner, the Specification of the '437 patent neither defines "intact amnion," nor indicates the amount of decellularization that takes place during the claimed process, and it unequivocally fails to disclose up to 90% decellularization, which Patent Owner would like us to read into the claim.

Patent Owner relies on the testimony of Petitioner's declarant, Dr. Jones, to support its construction. Although the testimony of Dr. Jones in this proceeding, as well as in the related district court proceeding, supports the proposition that a small amount of cells may be lost during the process of forming the graft, it does not support that up to 90% of the cells may be lost.

In particular, we observe that, in response to a question of whether the epithelial layer would be removed when the steps of claim 1 of performed on an amniotic membrane, Dr. Jones testified that the cellular layer may not be

maintained throughout the process, and that the process would alter the layer to some extent. Ex. 2027, 191:23–193:21. Dr. Jones testified also in response to questions about the process of Klen that the amount of cells that would be lost is not quantifiable, as it would vary. *Id.* at 266:4–267:8.

Thus, Dr. Jones' testimony supports the construction we adopted during institution, that is, claim 1 does not require that the dehydrated, laminated tissue graft contain an intact amnion. Rather, consistent with our Decision on Institution, claim 1 only requires that the dehydrated tissue graft product may be produced by a process in which intact amnion is subject to the washing, cleaning, laminating, and drying steps recited in the claim. Dr. Jones' testimony does not support adding to that construction that up to 90% of the cellular layer may be lost, and still fall within the scope of the claim.

Patent Owner relies also on the prosecution history of the '437 patent to support its construction. We acknowledge that the prosecution history is relevant to the claim constriction analysis. *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2016) ("The PTO should also consult the patent's prosecution history in proceedings in which the patent has been brought back to the agency for a second review."). In this case, however, we conclude that the prosecution history contradicts other more probative evidence of record, including the Specification. Moreover, Patent Owner asks us to accept certain parts of the prosecution history, but ignore others as a misstatement by the Examiner.

Specifically, in an interview summary, the Examiner stated that "[p]oints of note include that the method does not include any decellularization steps- thus both the epithelial layer and the fibroblast

cellular layer pf the amnion membrane must remain intact." Ex. 1002, 38.

In the "Reasons for Allowance," the Examiner stated:

> The instant claims are drawn to a tissue graft which is defined by its method of production. In these claims the method of production imparts the following unique structural characteristics to the claimed tissue graft: (1) *the claimed tissue graft consists of only two layers: an amnion and a chorion*; (2) *as there are no decellularization steps in the method, the amnion retains each of the original cellular layers, i.e. the epithelial layer and the cellular fibroblast layer*; (3) *the tissue graft is substantially free of blood and spongy/connective tissue, as per the step of "washing and substantially cleaning"*. With regards to the "washing and substantially cleaning" step, *it is submitted that the specification makes it clear that this washing and cleaning only achieves removal of blood and the spongy/connective layer, not actual cellular layers of either of the amnion or chorion layers. Thus, the tissue graft covered by the instant claims consists of a fully cellularized amniotic membrane (i.e. including the epithelial layer and the cellular fibroblast layer), and a fully cellularized chorionic membrane*, which are laminated together and dehydrated to form a unitary graft structure, wherein the tissue graft is substantially free of blood and spongy/connective tissue.
>
> The tissue graft as instantly claimed differs from natural full-thickness placenta which has been dehydrated because natural full-thickness placenta also contains a spongy/connective tissue layer between the amnion and the chorion; the instant claim excludes this, as it is limited to "consisting of" only the amnion and chorion membranes. The tissue graft as instantly claimed differs from the biofabric suggested by Hariri (of record), in that the tissue graft of the instant claims are not decellularized (i.e. they contain all cells of the amnion and chorion), whereas the biofabric of Hariri are fully decellularized. Finally, the tissue graft as instantly claimed differs from the tissue graft claimed in co-pending application 12/428,908 in that the tissue graft as instantly claimed includes the epithelial layer of the amnion, whereas the claimed tissue graft of the '908 application is de-epithelialized.

Id. at 28–29 (emphasis added).

Thus, the prosecution history does not support that up to 90% of the cells may be lost during performance of the recited process. Rather, the prosecution history suggests that the claim requires that the amniotic membrane remain fully cellularized, that is, no cells are lost, even during washing. Counsel for Patent Owner asks us to treat that as a misstatement on the part of the Examiner, arguing what the Examiner actually meant is that the claims do not require a decellularization step. Tr. 30. Patent Owner's explanation is unconvincing, however, as the Examiner had already discussed that there was no decellularization step in the method, before going on to further state that the product contained "a fully cellularized amniotic membrane (i.e. including the epithelial layer and the cellular fibroblast layer), and a fully cellularized chorionic membrane." Ex. 1002, 28–29.

Although we cannot agree with Patent Owner that the Examiner's remarks that the amnion and chorion must remain "fully cellularized" throughout the claimed process was a mere misstatement, we nevertheless observe that such a requirement for full cellularization contradicts the evidence of record in the instant proceeding, as both parties appear to agree that there may be some cell loss in the performance of the steps of claim 1. *See*, *e.g.*, Tr. 28 (Counsel for Patent Owner noting that "you may remove some cells via washing, cleaning, delamination.").

We conclude that Patent Owner has not pointed to any support for its proposed construction that "the amnion layer in the final product must, at a minimum, not have undergone substantial decellularization (*i.e.* removal of more than 90% of cells from the amnion layer of the graft)." PO Resp. 8–9.

Rather, we construe "intact amnion" as we did in the Decision on Institution, that is, not as requiring that the amnion be intact in the final product, but that as requiring only that the dehydrated tissue graft that may be produced by a process in which intact amnion is subject to the washing, cleaning, laminating, and drying steps as set forth in challenged claim 1. That would encompass any decellularization that would naturally occur in the performance of those steps, but the record does not support quantifying that decellularization as being no greater than 90%.

ii. "washing and substantially cleaning"

Petitioner requests that this claim be construed as reducing the amount of blood clots and other extraneous tissue found in the native amnion and chorion layer." Pet. 4 (citing Ex. 1005).

Patent Owner did not respond to Petitioner's proposed construction in its Preliminary Response, but requests that we construe the claim limitation of "washing and substantially cleaning" in its Response. PO Resp. 12–17. In particular, Patent Owner contends that Petitioner appears to be construing this phrase as requiring the removal of any amount of blood clots and spongy/connective tissue, which, Patent Owner asserts, reads "substantially" out of the claim. *Id.* at 13. Patent Owner argues further that Petitioner's construction "is contrary to the plain language of the claims, the prosecution history, and the understanding of one of skill in the art, all of which indicate that the washing and substantially cleaning step removes a substantial portion of the spongy layer." *Id.* (citing Ex. 2025 ¶¶ 100, 102–110). According to Patent Owner, "[i]n light of the claims, specification, file history, and testimony of Petitioner's own expert, 'washing and substantially cleaning' requires substantial removal of blood clots and spongy/connective

tissue, *i.e.* the tissue that forms the intermediate layer of a placenta." *Id.* at 11–12.

In particular, Patent Owner points to the declaration of Petitioner's declarant, Dr. Jones, submitted in the related district court proceeding. *Id.* at 13–14. Dr. Jones stated that the "plain claim language [] explicitly requires that the amnion/chorion be ***substantially*** cleaned." *Id.* at 13 (quoting Ex. 2025 ¶ 100). Dr. Jones opined in that declaration that "a construction that does not attempt to describe the amount of 'blood clots and other extraneous tissue' that must be removed to satisfy the claim limitation, fails to account for the express requirement that the tissue be '***substantially*** cleaned.'" *Id.* at 14 (quoting Ex. 2025 ¶ 100). Patent Owner states it agrees with the declaration of Dr. Jones submitted in the related district court proceeding, asserting that "the requirement of substantial cleaning must thus be more than a mere washing step (such as mere submerging in water or saline solution) that removes any portion of the spongy layer, no matter how insignificant." *Id.*

Patent Owner argues that Petitioner and Dr. Jones are now advocating a construction that reads "substantially cleaning" out of the claims. In fact, Patent Owner asserts, Dr. Jones admitted as much during her deposition, stating that she did not think there was a difference between washing and substantially cleaning. *Id.* at 15 (citing Ex. 2027, 119:21–120:2, 150:10–24, 152:23–153:11, 271:20–272:5).

Patent Owner argues further that the prosecution history supports its construction. *Id.* at 15 (citing Ex. 1002, 51–52, 60). Patent Owner notes that the Notice of Allowability explicitly states "that 'the tissue graft covered by the instant claims . . . is ***substantially free of blood and***

spongy/connective tissue.'" *Id.* at 16 (quoting Ex. 1002, 29). In fact, Patent Owner asserts, Dr. Jones in her declaration in the district court proceeding relied on that prosecution history in asserting that the washing and cleaning steps included removal of the spongy/connective tissue. *Id.* at 15–16 (citing Ex. 2025 ¶¶ 103–104).

Petitioner responds that the construction for "washing and substantially cleaning" that Patent Owner for the first time advocates in its Response "is contrary to the claim construction it previously advanced . . . [in] the Federal District Court in the Related Litigation." Reply 2–3.[4]

Petitioner argues further that Patent Owner's proposed construction is not consistent with the Specification. *Id.* at 4–5. Petitioner asserts that the Specification does not refer to the "spongy layer," and never discloses that a "substantial" portion of it should be removed during the washing and cleaning step. *Id.* at 4. Although the Specification teaches cleaning the layers to remove "extraneous tissue," Petitioner asserts that Patent Owner does not offer any evidence that the ordinary artisan would consider the spongy tissue to be extraneous. *Id.* In fact, Petitioner avers, Patent Owner's declarant, Dr. Baergen, in a declaration submitted in the district court proceeding, has stated that the spongy layer is considered to be part of the amnion or the chorion. *Id.* (citing Ex. 1006 ¶ 118). Moreover, Dr. Baergen also stated in that declaration that examples of extraneous tissue include

[4] Petitioner also contends that the claim interpretation is inconsistent with the claim interpretation Patent Owner advanced in IPR2015-00320. That *inter partes* review, however, involved a different patent and different claim language. Thus, Patent Owner's proposed construction in that proceeding is not relevant to the claim language of "washing and substantially cleaning," and we need not further address Petitioner's arguments in this regard.

"'blood clots, remnants of tissue from various pathological states, [and] dead tissue'- but not spongy tissue." *Id.* at 5 (quoting Ex. 1006 ¶ 111). Finally, Petitioner asserts that its Declarant, Dr. Jones, was asked to apply the construction offered by Patent Owner in the related district court proceeding. *Id.* at 6 (citing Ex. 1010 ¶¶ 20–21).

As noted by Petitioner (Reply 4), the Specification does not state anything about removal of the spongy layer. Rather, the Specification teaches:

> Care is then taken to *remove blood clots and other extraneous tissue* from each layer of tissue until the amniotic membrane tissue and the chorion are clean and ready for further processing. More specifically, the amnion and chorion tissues are placed on the processing tray and *blood clots* are carefully removed using a blunt instrument, a finger, or a sterile non-particulating gauze, *by gently rubbing the blood until it is free from the stromal tissue of the amnion and from the trophoblast tissue of the chorion*. . . . . Using a blunt instrument, a cell scraper or sterile gauze, *any residual debris or contamination is also removed*.

Id. at 6:42–62 (emphasis added). Thus, it is clear that the washing and substantial cleaning step removes blood clots. The issue becomes, therefore, what is meant by extraneous tissue. From the passage quoted above, extraneous tissue appears to be referring to "residual debris or contamination," and not the spongy later, which is part of the placenta.

In the related district court proceeding, Dr. Jones, Petitioner's declarant, took the position that "substantially cleaning" required removal of the spongy/connective tissue, consistent with the Examiner's statement during prosecution of the '437 patent. Ex. 2027 ¶¶ 100, 103–105.

Patent Owner's expert, Dr. Baergen, however, opined that the "washed and substantially cleaned" claim language of the '437 patent "is

directed to reducing the amount of blood clots and other extraneous tissue found in the native amnion and native chorion layers." Ex. 1006 ¶ 1009. Citing the portion of the Specification of the '439 quoted above, Dr. Baergen testified that interpretation was consistent with the teachings of the Specification. *Id.* ¶ 111. In particular, Dr. Baergen noted:

> [O]ne of ordinary skill in the art, in light of the specification and his knowledge and experience, would have understood that separating the native amnion and native chorion would disrupt the native intermediate spongy layer. The native intermediate spongy layer is . . . the border of the native amnion and native chorion. Histologically, some have classified this layer as part of the amnion while others have classified it as part of the chorion. Regardless, it is the presence of this intermediate spongy layer that allows native amnion and chorion to slide against each other. In the context of the claimed invention, one of ordinary skill in the art would have understood that the methods disclosed in the specification would lead to separation of the native amnion from native chorion, so that the native amnion and native chorion would peel apart within the intermediate spongy layer . . . . As the separation occurs through intermediate spongy layer, by virtue of the separation, the intermediate spongy layer as a layer in native form is destroyed. But, a portion of the intermediate spongy layer would stay attached on the separated amnion and some of it would stay attached on the separated chorion, *i.e.*, some portion or remnant of the intermediate spongy layer would get stuck on both the separated chorion and the separated amnion.

Id. ¶ 118.

In fact, Dr. Baergen opined:

> [O]ne of ordinary skill in the art would have understood that a *complete removal of the native "spongy/connective" layer is virtually impossible*. That is because, as discussed above, the intermediate spongy layer is at the junction of the native amnion and native chorion. Once the native amnion and chorion are separated in accordance with the invention, the separation occurs

> within the intermediate spongy layer, and thus, some portion necessarily gets stuck on each of the separated amnion and separate chorion layers. As such, it is nonsensical to contend that little or close to zero spongy/connective tissue remains in the tissue graft. Rather, because of the inherent properties of the separated amnion and chorion membrane, the spongy/connective tissue is necessarily a part of the claimed tissue grafts

Id. ¶ 119 (emphasis added).

We conclude that Dr. Baergen's testimony is most consistent with the teaching of the Specification that blood clots and extraneous tissue, such as debris and contaminants, are removed. Thus, we decline to construe "washing and substantially cleaning" as requiring removal of the spongy layer.

We have considered the prosecution history of the '437 patent, but it does not convince us otherwise. As discussed above in our discussion of the construction of "intact amnion," Patent Owner asks us to give credence to certain portions of the prosecution history, but to discount other portions as misstatements. Moreover, the Examiner stated that "the specification makes it clear that this washing and cleaning only achieves removal of blood and the spongy/connective layer, not actual cellular layers of either of the amnion or chorion layers." Ex. 1002, 28–29. But, as we have already discussed, the Specification makes no mention of the spongy layer.

Thus, we construe "washing and substantially cleaning" as requiring removal of substantially all blood clots, debris, and contamination from the amnion and chorion layers. We do not construe it as requiring removal of substantially all of the spongy layer.

iii. "laminating the amnion and chorion layer together"

In its response, Patent Owner argues that "laminated" and "laminating" should be construed as requiring that the separated washed amnion and /or chorion layers be adhered together. PO Resp. 17. In our Decision on Institution, we agreed, and construed "laminate," "laminated," or "laminating" as requiring that the amnion and/or chorion layers be adhered together. Dec. Inst. 8. Petitioner does not argue that construction in its Reply, and we see no reason to depart from that construction. Thus, consistent with the Decision on Institution, we construe "laminate," "laminated," or "laminating" as requiring that the amnion and/or chorion layers be adhered together.

iv. Other Claim Terms

We determine for purposes of this Final Written Decision that none of the remaining terms in the challenged claims requires express construction. *See, e.g. Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (noting that only claim terms that are in controversy need to be construed, and then only to the extent necessary to resolve the controversy).

B. Principles of Law

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 (1966). The level of ordinary skill in the art usually is evidenced by the references themselves. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

For an obviousness analysis, prior art references must be "considered together with the knowledge of one of ordinary skill in the pertinent art." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (quoting *In re Samour*, 571 F.2d 559, 562 (CCPA 1978)). Moreover, "it is proper to take into account not only specific teachings of the reference, but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). That is because an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see also Translogic*, 504 F.3d. at 1259.

Like our reviewing court, "[w]e will not read into a reference a teaching away from a process where no such language exists." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1364 (Fed. Cir. 2006). Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the invention. "A statement that a particular combination is not a preferred embodiment does

not teach away absent clear discouragement of that combination." *Syntex (USA) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). "The fact that the motivating benefit comes at the expense of another benefit . . . should not nullify its use as a basis to modify the disclosure of one reference with the teachings of another. Instead, the benefits, both lost and gained, should be weighed against one another." *Medichem, S.A. v. Rolabo S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (citations omitted).

C. Obviousness over the Combination of Klen (Ex. 1013) and Sulner (Ex. 1015)

Petitioner asserts that claims 1 is unpatentable as being rendered obvious by the combination of Klen and Sulner. Pet. 26–28; *see also id*. at 12–24 (discussing the teachings of Klen). Patent Owner disagrees. PO Resp. 31–43.

i. Overview of Klen (Ex. 1013)

Klen discloses a method of preparing chorion and/or amnion grafts for use in treating burns. Ex. 1013, 289. As taught by Klen, "[n]ormal placenta of healthy parturients are used for the preparation of amnion, chorion and combined amnion-chorion grafts." *Id.* Amnion and chorion are separated, and are submerged into saline to wash away the majority of blood clots. *Id.* The membranes are then stretched on arranged stripes of plastic net, cut into the shape of strips, and are covered with Tylexol and rolled up. *Id.* at 289–90. The rolls are inserted into a vessel with sterile nitrogen until enough membranes are collected for the freeze-drying process. *Id.* at 290. The freeze-drying process is performed under vacuum at a maximum temperature of 39°C for a period of twenty-four hours. *Id.* The vacuum is replaced by sterile nitrogen, and the graft is stored at room temperature in a cool, dark place.

According to Klen:

> [G]rafts prepared within two hours after delivery are more successful than those prepared after a longer period. With the greatest probability it gives evidence for the fact that the effective complex of substances is highly sensitive and undergoes undesirable changes quite easily. It has resulted in the instruction to perform the preparation after the delivery as soon as possible. The second statistical datum concerns the storage of the preserved rolls up to the time when they are freeze-dried. We have proved that after freezing at the temperature of -25 degrees C lasting for a longer period than a week, the grafts are less successful than those frozen for a shorter period. This fact again has given evidence concerning the sensitivity of the effective complex of healing substances and has led us to store the preserves prepared for drying in a place with a deeper temperature and, first of all, to perform freeze-drying as early as possible.

Id. at 290–91.

ii. Overview of Sulner (Ex. 1015)

Sulner is drawn to a method of preparing a tympanic membrane using a collagen biofabric. Ex. 1013 ¶ 2. The collagen biofabric may be made from a human placenta. *Id.* ¶ 214. According to Sulner:

> The collagen biofabric may be used in a single-layered format, for example, as a single-layer sheet or an un-laminated membrane. Alternatively, the collagen biofabric may be used in a double-layer or multiple-layer format, e.g., the collagen biofabric may be laminated. Lamination can provide greater stiffness and durability during the healing process.

Id. ¶ 33.

iii. Analysis

Petitioner relies on Klen for teaching amnion grafts, chorion grafts, and combined amnion-chorion grafts, as well as a process of producing such

grafts. Pet. 12. In particular, Petitioner notes that Klen teaches amnion, chorion, and combined amnion-chorion grafts that are dried. *Id.* at 13.

Petitioner contends also that Klen teaches the step of "isolating an intact amnion layer," which it refers to as "element B" or "Elm. B." *Id.* at 13–19. In particular, Petitioner notes that Klen does not teach a step of decellularizing the amnion, but observes that a small number of cells may be removed by one or more of the steps of Klen, such as the washing step. *Id.* at 18.

According to Petitioner, Klen also discloses the step of isolating a chorion layer, which it refers to as "Elm. C." *Id.* at 19. Petitioner notes that Klen teaches amnion only grafts, chorion only grafts, as well as amnion-chorion grafts. In order to make the amnion-only or chorion-only grafts, Petitioner observes that the amnion and chorion must be separated, and, thus, necessarily includes a step of isolating the chorion layer." *Id.* (citing Ex. 1010 ¶¶ 69, 77).

Petitioner asserts also that Klen teaches a step of "washing and substantially cleaning the amnion layer and the chorion layer," which it refers to as "Elm. D." *Id.* at 19–21. In particular, Petitioner notes that "Klen teaches that '[t]he membranes are submerged into the saline[,] ***washing away the majority of blood-clots***" (emphasis added) Ex. 1013, 4, which constitutes "washing and substantially cleaning the amnion layer and the chorion layer.'" *Id.* at 20 (citing Ex. 1010 ¶79).

Petitioner notes that according to the declaration of Dr. Baergen submitted by Patent Owner in the related district court proceeding, "these extraneous tissues may include 'the remnants of tissue from various pathological states and/or dead tissue.'" *Id.* (quoting Ex. 1006 ¶ 111).

According to Petitioner, the ordinary artisan would understand that such tissue would be unsafe and undesirable for use in a tissue graft, but would also be easily removed as compared to non-extraneous tissue. *Id.* (citing Ex. 1010 ¶ 81). Such tissue, Petitioner asserts, would, thus, be necessarily removed by submerging the membranes in saline and washing those tissues away before any further processing. *Id.* (citing Ex. 1010 ¶ 81).

As to the step of "dehydrating the laminated graft to produce the dehydrated, laminated tissue graft," which Petitioner refers to as "Elm. F," Petitioner explains that "Klen discloses that the amniotic and chorionic membranes are 'cut along the shape of … [arranged] stripes' of a plastic net, and stretched on arranged stripes of a plastic net to '***facilitate drying'*** of the membranes." *Id.* at 23 (citing Ex. 1013, 4–5). Petitioner notes that Klen teaches further "that the grafts are 'covered by Tylexol [a thin tulle mesh material] and rolled up, . . . inserted into vessels . . . ***and then stored under deep temperature up to the time when sufficient quantity of preserves for freeze-drying is collected***.'" *Id.* (quoting Ex. 1013, 5). Petitioner asserts that the ordinary artisan understands that freeze-drying is a dehydration process. *Id.* (citing Ex. 1010 ¶ 88).

Petitioner addresses also the use of the transitional phrase "consisting of" in claim 1. *Id.* at 23–24. Specifically, Petitioner contends that because "the Klen process includes, and only includes, the isolating, washing and substantially cleaning, laminating and dehydrating steps of Claim 1, Klen satisfies the 'consisting of' language of Claim 1." *Id.* at 24.

Petitioner contends that "[t]o the extent that Klen does not explicitly disclose a 'laminating step' *per se*, Claim 1 would still be unpatentable because it is obvious over Klen in view of Sulner." *Id.* at 26. Petitioner

relies on Sulner for teaching laminating two layers of a placental graft together to provide greater stiffness and durability during the healing process. *Id.* Thus, Petitioner contends, Sulner provides a reason to laminate the amnion and chorion layers together of the amnion-chorion graft of Klen, as lamination would provide a more durable graft. *Id.*

Patent Owner responds that Klen fails to disclose all the elements of claim 1. PO Resp. 31. Specifically, Patent Owner argues that "Klen fails to disclose at least (i) washing and substantial cleaning of the amnion and chorion layers and (ii) lamination of isolated amnion and chorion layers, as required by Claim 1." *Id.* at 32.

As to the washing and substantially cleaning step required by claim 1, Patent Owner argues that Klen teaches only that its proposed tissue graft is submerged in saline. *Id.* at 33 (citing Ex. 1013, 289; Ex. 2030 ¶¶ 58, 97; Ex. 2027, 246:22–247:23). Petitioner argues, however, that "Klen does not teach a duration of time of that submersion, a temperature range for the saline solution, or the addition of a physical component of the washing and cleaning process, such as agitation, mechanical scraping, or use of a finger or gauze." *Id.* (citing Ex. 2027, 247:24–250:1; Ex. 2030 ¶¶ 58–98). Klen teaches only that a majority of the blood clots are removed. *Id.* (citing Ex. 1013, 289; Ex. 2030 ¶ 97; Ex. 2027, 249:9–250:1). According to Patent Owner, as admitted by Dr. Jones, "Klen is silent with respect to whether any of the spongy/intermediate layer would be removed and, if so, how much of that layer would be removed or why it should be removed." *Id.* (citing Ex. 2027, 249:13–250:1, 251:2–6; 251:10–14, 278:23–279:18; Ex. 2030 ¶ 98).

In particular, Patent Owner argues that although Dr. Jones noted that the ordinary artisan would understand that, in addition to the blood clots, the

method of Klen would remove at least some additional tissues, "Dr. Jones admitted that there are instances where 'mechanical forces,' *e.g.* gauze, scraping, or agitation, would be needed to wash and substantially clean placental tissue. *Id.* at 33–34 (citing Ex. 1010 ¶ 62; Ex. 2027, 43:12–44:11, 45:15–46:2, 147:22–148:1). Moreover, Patent Owner asserts, "Dr. Jones admitted that she was unable to quantify the amount of extraneous tissue, *e.g.*, spongy/intermediate layer tissue, that would be washed away by submersion, other than 'at least some,'" and also admitted that "that the cleaning process taught by the '437 Patent was 'much more aggressive' than the mere use of saline disclosed in Klen." *Id.* at 34 (citing Ex. 2027 250:2-24, 278:23-279:3, 267:13-270:19; Ex. 2030 ¶ 100).

As we have construed "washing and substantially cleaning," above, that step does not require substantial removal of the spongy layer. Thus, although we have considered Patent Owner's arguments that Klen does not teach removal of the spongy layer, those arguments are not persuasive as claim 1 does not exclude tissue grafts containing a portion of the spongy layer.

Patent Owner argues[5] also that Sulner cannot remedy the deficiencies of Klen. PO Resp. 39. Specifically, Patent Owner contends that Petitioner cherry-picks the teachings of Sulner that support its obviousness challenge,

[5] We note that Patent Owner repeats its argument that Klen does not disclose laminating isolated amnion and chorion together. PO Resp. 35–38. As Patent Owner recognizes, however, that we agreed with it regarding that argument in the Decision on Institution. *Id.* at 35 (citing Dec. Inst. 12). As Petitioner does not contest that finding in its Reply, we see no need to revisit that argument in this Final Decision.

but ignores the teachings of Sulner that support substantial decellularization. *Id.*

Patent Owner contends that references such as Sulner and Hariri,[6] as well as other art, taught substantial removal of cells. *Id.* at 39–40 (citing Ex. 2030 ¶¶ 65–85; Ex. 2027, 317:4–318:20, 319:12–320:5, 324:2–4, 326:23–25, 330:5–14). According to Patent Owner, decellularization is preferred because decellularized placental grafts were believed to have reduced immunogenicity, and thus reduced rejection rates. *Id.* at 40 (citing Ex. 2027, 329:15–17, 338:7–24; Ex. 1034, 6 (Table 1)). Moreover, Patent Owner asserts that Dr. Jones testified that an exposed basement membrane provides for increased chemical reaction, facilitating tissue healing. *Id.* (citing Ex. 2026 ¶¶ 15, 29). Thus, Patent Owner avers, the ordinary artisan "based on the record evidence would believe there to be strong reasons to substantially decellularize placental tissue grafts, and no reason to do otherwise." *Id.* at 41 (citing a decision on institution in related *inter partes* reviews (Ex. 2028, 13, 16)).

Patent Owner argues further that Klen provides no reason to retain the cells of the amnion and/or the chorion. *Id.* at 38 (citing Ex. 2027, 252:25–253:8); *see also id.* at 41. Thus, Patent Owner asserts, "[e]ven if Klen inherently discloses a tissue graft with an intact epithelial or fibroblast cellular layer, Klen provides no reason to maintain cellularity of any layer, much less an epithelial or fibroblast cellular layer in a placental tissue graft." *Id.* at 39.

[6] Hariri et al., Pub. No. US 2003/0187515 A1, published Oct. 2, 2015 A1 (Ex. 1018) ("Hariri").

Patent Owner argues, therefore, if the ordinary artisan were to combine Sulner with Klen "to improve the Klen reference," one would have removed substantially all the cells of the graft of Klen. *Id.* at 41. Patent Owner asserts, therefore, that "Sulner explicitly teaches away from the claimed invention which, as set forth above, excludes a graft that has gone through substantial decellularization." *Id.* at 42. In that regard, we note that Patent Owner contends that the conventional wisdom at the time of the invention was to substantially decellularize placental tissue grafts, as taught by Sulner and Hariri. *Id.* at 20–30.

Patent Owner's arguments do not persuade us that the ordinary artisan would not have combined Klen and Sulner to arrive at the graft of claim 1. Patent Owner acknowledges that the graft of Klen is not decellularized. Tr. 30 (Counsel for Patent Owner agreeing that Klen does not disclose a decellularization step). We acknowledge that Sulner teaches decellularization of the graft such that the generation of new immunological sites is limited (ex. 1015 ¶ 220), but that does not amount to a teaching away of not performing a decellularization step. *See Baxter Int'l, Inc. v. McGaw, Inc.*, 149 F.3d, 1321, 1328 (Fed. Cir. 1998) (noting that in general, "a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant."); *see also Medichem*, 437 F.3d at 1165 (noting that benefits, both lost and gained, may be weighed against each other). Here, Klen specifically teaches that its grafts may be used in the treatment of burns, and also notes that the grafts have been used with good results in treating skin defects caused by leprosy, in ophthalmology at burns of the cornea, and in varicose ulcers. Ex. 1013, 290.

"[T]he test [for obviousness] 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). In addition, a reference disclosure is not limited only to its preferred embodiments, but is available for all that it discloses and suggests to one of ordinary skill in the art. *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976). Thus, we conclude that the combination of Klen and Sulner would render obvious both a graft that was performed by a process that includes a decellularization step, as well as a graft that does not include such a decellularization step, such as the graft of Klen.[7]

As to Patent Owner's arguments that it was conventional wisdom to decellularize a placental graft, we reiterate that Klen teaches a graft that has not been decellularized, and thus the evidence demonstrates that such grafts were known and used. Moreover, as Patent Owner conceded, the Specification of the '437 patent has no discussion of decellularization. Thus, the Specification of the '437 patent itself does not support Patent Owner's argument that the lack of a decellularization went against conventional wisdom.

[7] We note that during oral argument, Patent Owner argued that it maintains that the ordinary artisan would not have a reason to combine Klen and Sulner as set forth in its Preliminary Response, but acknowledged that it had not repeated those arguments in its post-institution Patent Owner Response. Notwithstanding a misstatement by a panel member during argument (Tr. 61), although there is not a rule against maintaining arguments from the Preliminary Response, the Scheduling Order does state that "any arguments for patentability not raised in the response will be deemed waived." Paper 14, 3. Moreover, as set forth in the Decision on Institution, the Petition provides a reason for combining Klen and Sulner. Pet. 26. That is, laminating layers of amnion and chorion together provides greater stiffness and durability during the healing process. Dec. Inst. 15.

After considering Petitioner's arguments and evidence, as well as the evidence and arguments presented by the Patent Owner in response, we agree with Petitioner and are persuaded that the Petition demonstrates by a preponderance of the evidence the unpatentability of claim 1 over the combination of Klen and Sulner.

D. Obviousness over the Combination of Klen (Ex. 1013), Sulner (Ex. 1015), and Tseng (Ex. 1011)

Petitioner contends that claim 2 is unpatentable as obvious over the combination of Klen, Sulner, and Tseng. Pet. 50–51. Patent Owner disagrees. PO Resp. 43–47.

i. Overview of Tseng (Ex. 1011)

Tseng is drawn to "amniotic membrane grafts especially usable in the repair of injured eyes." Ex. 1011, 1:16–17. Tseng teaches that the amnion is histologically composed of five layers. *Id.* at 3:49. According to Tseng, the "avascular stromal contains fetal mesenchyme and includes the compact layer, fibroblastic layer and spongy layer." *Id.* at 3:51–53.

In preparing the graft of Tseng, placenta is rinsed with balanced saline, which preferably contains antibiotics, which aid in the cleaning and preservation process, 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. Analysis

Petitioner relies on the combination of Klen and Sulner in the manner discussed above with respect to claim 1. Pet. 60. Claim 2 requires that the washing step of claim 1 be carried out in an antibiotic solution, and relies on Tseng for teaching such a step. *Id.* at 59–60. Petitioner relies on Tseng for its teaching of performing the washing step in an antibiotic solution. *Id.* at 60. According to Petitioner, it would have been obvious to perform such as washing step to clean more effectively the membrane of contaminates. *Id.* at 59 (citing Ex. 1011, 4:64–65).

Patent Owner responds, in essence, that Tseng does not remedy the deficiencies of the combination of Klen and Sulner. PO Resp. 43. In fact, Patent Owner asserts, Tseng provides further reasons to decellularize the graft, although Tseng proposes killing the cells, rather than removing them. *Id.* at 43–44 (citing Ex. 2030 ¶¶ 117–118). The arguments of Patent Owner in this regard are not persuasive for the reasons set forth above for the reasons set forth above in the analysis of the combination of Klen and Sulner.

Patent Owner contends further that even if one were to combine Klen, Sulner, and Tseng, the ordinary artisan would have cryopreserved the resulting graft. PO Resp. 46. Specifically, Patent Owner argues that Tseng teaches the benefits of cryopreservation, and thus, "directly teaches away from the freeze dried tissue graft of Klen and the heat dehydrated tissue graft of Sulner." *Id.* at 46–47 (citing Ex. 2030 ¶ 130). Patent Owner avers,

therefore, that the combination of Klen, Sulner, and Tseng does not render challenged claim 2 obvious. *Id.* at 47.

We are unpersuaded. Each of Klen, Sulner, and Tseng teach different ways of preparing a placental tissue graft, and evidence that the use of any one of those methods would have been known to the ordinary artisan. Moreover, "[t]he 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." *Keller*, 642 F.2d at 425. Thus, the ordinary artisan would understand that the use of an antibiotic in the wash solution to more effectively clean contaminants also requires that the graft be cryopreserved.

E. Patent Owner's Motion to Exclude

Patent Owner asks us to exclude Exhibits 1056–1059, 1064, 1065 and 1068-1070 (Paper 38, 1), Exhibits 1056, 1061, 1063 and 1067-1074 (*id.* at 2), as well as those portions of pages 15–17, 19, and 20 of Petitioner's Reply that address those exhibits. Patent Owner's Motion to Exclude is dismissed as moot, as we did not rely on those exhibits in this Final Written Decision.

III. CONCLUSION

After considering Petitioner's and Patent Owner's positions and evidence, we conclude that Petitioner has demonstrated by a preponderance of the evidence that claim 1 of the '437 patent is unpatentable under 35 U.S.C. § 103(a) over the combination of Klen and Sulner. We conclude further that Petitioner has demonstrated by a preponderance of the evidence

that claim 2 of the ’437 patent is unpatentable under 35 U.S.C. § 103(a) over the combination of Klen, Sulner, and Tseng.

IV. ORDER

Accordingly, it is hereby:

ORDERED that Petitioner shown by a preponderance of the evidence that claims 1and 2 of the ’437 patent are unpatentable under 35 U.S.C. § 103(a);

FURTHER ORDERED that Patent Owner’s Motion to Exclude (Paper 38) is dismissed as moot; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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