

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

EMBODY, INC. and ZIMMER BIOMET HOLDINGS, INC.,
Petitioner.

v.

LIFENET HEALTH,
Patent Owner.

IPR2025-00249
Patent 11,318,227 B2

Before MICHAEL J. FITZPATRICK, ANNETTE R. REIMERS, and
CHRISTOPHER C. KENNEDY, *Administrative Patent Judges*.

FITZPATRICK, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining Some Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

Embody, Inc. and Zimmer Biomet Holdings, Inc. (collectively, “Petitioner”) filed a Petition requesting *inter partes* review of claims 1–8 of U.S. Patent No. 11,318,227 B2 (Ex. 1001, “the ’227 patent”) pursuant to 35 U.S.C. § 311(a). Paper 2 (“Petition” or “Pet.”). Patent Owner, LifeNet Health, filed a Preliminary Response pursuant to 37 C.F.R. § 42.107(b). Paper 8 (“Prelim. Resp.”). We granted the Petition. Paper 13 (“Inst. Dec.”).

During the review, Patent Owner filed a Patent Owner Response (Paper 23 (“PO Resp.”)), Petitioner filed a Reply (Paper 26 (“Pet. Reply”)), and Patent Owner filed a Sur-Reply (Paper 29 (“PO Sur-Reply”)). Pursuant to our authorization, the parties filed papers identifying alleged improper Reply and Sur-Reply arguments and evidence, and responses to those papers. Papers 27, 28, 34, and 35. An oral hearing was held on May 6, 2026, and a transcript of the hearing is included in the record. Paper 40 (“Tr.”).

We have jurisdiction under 35 U.S.C. § 6, and this Final Written Decision, issued pursuant to 35 U.S.C. § 318(a), addresses issues and arguments raised during the review. For the reasons discussed below, we determine that Petitioner has proven, by a preponderance of the evidence, that claims 1 and 4–8 of the ’227 patent are unpatentable but has failed to prove that claims 2 and 3 are unpatentable.

A. Real Parties in Interest

Petitioner identifies Embody, Inc. as the real party in interest. Pet. 2. Petitioner further identifies Zimmer Biomet Holdings, Inc. (“ZBH”) as a second real party interest “[o]ut o[f] an abundance of caution.” *Id.* at 3. Patent Owner identifies itself as the sole real party in interest. Paper 3, 1.

B. Related Matters

The parties identify *LifeNet Health v. Zimmer Biomet Holdings, Inc.*, Case No. 2:23-cv-00479 (E.D. Va.) as a related matter. Pet. 3; Paper 3, 1. Petitioner also filed a petition for *inter partes* review for related U.S. Patent No. 10,137,223 B2 in IPR2025-00248.

C. The '227 Patent

The '227 patent is titled “ALIGNED FIBER AND METHOD OF USE THEREOF.” Ex. 1001, code (54). The '227 patent issued from Application No. 16/045,159, which was filed on July 25, 2018. *Id.* at codes (21), (22). The '227 patent claims priority to Application No. 14/776,106, filed March 13, 2014, and provisional Application No. 61/785,031, filed on March 14, 2013. *Id.* at codes (21), (60).

The '227 patent discloses a “scaffold comprising an aligned fiber” used for tissue engineering. *Id.* at 1:23–35. It describes the use of an electrospinning apparatus to create fibers as small as one nanometer that are aligned in one principal direction, rather than being randomly oriented. *Id.* at 2:42–44. This electrospinning apparatus includes one or more spinnerets that are used to extrude a polymer or oligomer solution to form fibers. *Id.* at 3:18–22. As a result of the electrospinning, the fibers may be aligned at a particular angle. *Id.* at 5:4–18.

The '227 patent further describes the use of fast Fourier transform (FFT) analysis to measure the degree of alignment of the electrospun fibers. *Id.* at 13:25–49. Specifically, the '227 patent indicates that the FFT analysis may be performed using the methods described in Chantal Ayres *et al.*, “*Measuring fiber alignment in electrospun scaffolds: a user’s guide to the 2D fast Fourier transform approach*” 19 J. BIOMATERIALS SCI., POLYMER

EDN 603–621 (2008) (“Ayres 2008”; Ex. 1010), which is incorporated by reference into the ’227 patent.¹ Ex. 1001, 13:38–46. The ’227 patent explains that an FFT analysis of the aligned fibers may have “adjacent major peaks with about 180° apart from each other.” *Id.* at 13:25–28. The ’227 patent further states that “[t]he ‘major peaks’ herein refer to peaks higher than the average of the peaks in the result.” *Id.* at 13:28–29.

Figure 8A of the ’227 patent is reproduced below.

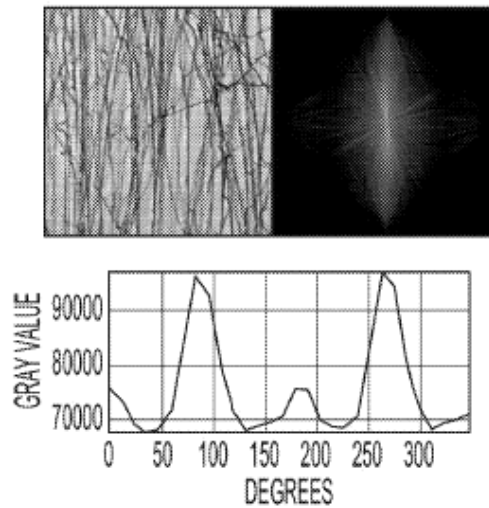


FIG. 8A

Ex. 1001, Fig. 8A. Figure 8A, reproduced above, includes three images and “depicts exemplary FFT analysis results of the [electrospun] fibers described” in the patent. *Id.* at 2:10–11; Ex. 2015 ¶51 (“The ’227 patent’s Figure 8A shows a FFT analysis result of aligned fibers.”).² The top left image above shows the electrospun fibers using a scanning electron

¹ Both parties agree Ayres 2008 is incorporated by reference into the ’227 patent. Pet. 11; PO Sur-Reply 4.

² Exhibit 2015 is a declaration by Patent Owner’s witness, Antonio G. Mikos, Ph.D.

microscope (SEM). Ex. 1001, 21:25–45.³ The top right image above shows the Fourier spectrum of the SEM image created using the “ImageJ64 FFT tool” reflecting a known pattern for aligned fibers. *Id.* at 21:40–45.⁴ The graph below those two images is a 2-dimensional FFT plot of the Fourier spectrum, showing major peaks at about 90° and 270° (i.e., about 180° apart) and smaller peaks at about 0° and 180°.

Figure 8B is reproduced below.

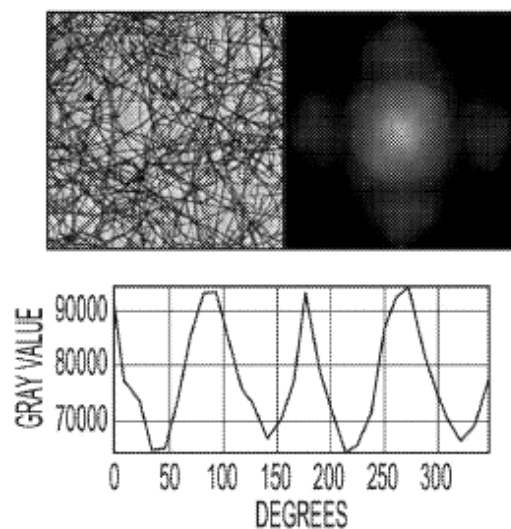


FIG. 8B

Ex. 1001, Fig. 8B. Figure 8B, reproduced above, includes three images and “depicts an FFT analysis of a control sample” of randomly oriented fibers. *Id.* at 2:12; *see also* Ex. 2015 ¶51 (“Figure 8B as shown [sic] a control sample, e.g., with random fibers.”). Here, the 2-dimensional FFT plot (bottom image) of the Fourier spectrum (upper right image) shows at least

³ The cited passage references Figure 3A, which shows the same image.

⁴ The cited passage references Figure 3B, which shows the same image.

three large but not uniform peaks at about 90°, 180°, and 270°, with the peak at about 180° being the shortest.⁵

The '227 patent indicates that a variety of natural or synthetic materials may be used alone or blended to form aligned fibers according to the electrospinning techniques described therein. *Id.* at 7:35–55.

D. The Challenged Claims

Petitioner challenges claims 1–8 of the '227 patent. Claims 1 and 7 are independent and reproduced below:

1. A method of treating a tissue defect in a subject comprising

implanting at the tissue defect a scaffold comprising crosslinked fibers comprising collagen, wherein a result of a fast Fourier transform (FFT) analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other, and

applying the scaffold to the tissue defect to repair a tendon, a ligament or a nerve defect.

7. A method of cell culture comprising

placing cells on a scaffold comprising aligned fibers, wherein a result of a FFT analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other, and

growing the cells in conditions suitable for the cell culture.

Ex. 1001, 23:29–37, 24:5–11.

⁵ Figure 8B may also show a fourth large peak at about 0°, but it is difficult to discern precisely where and even if the plot peaks at about 0°.

E. The Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claim(s) Challenged	35 U.S.C. §⁶	Reference(s)/Basis
1–6	103	Huang ² , Kuo
1–6	103	Lee, Kuo
7, 8	102	Huang ²

II. ANALYSIS

A. Level of Ordinary Skill in the Art

Petitioner proposes that a person of ordinary skill in the art (“POSITA”) “would be a Ph.D. student with a minimum of two years of experience in their faculty advisor’s laboratory” and would have an understanding of “electrospinning fibers, including for tissue engineering, tissue engineering techniques, and using/performing FFT analysis.” Pet. 20–21 (citing Ex. 1003 § II.C⁷). Patent Owner does not dispute Petitioner’s proposal but specifies the set of disciplines within which the Ph.D. would have been earned, namely “bioengineering, chemical engineering, mechanical engineering, or a related engineering discipline.” PO Resp. 6.

We adopt and apply Petitioner’s proposal as clarified by Patent Owner regarding the Ph.D. discipline.

⁶ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, which was enacted September 16, 2011, amended 35 U.S.C. §§ 102 and 103. AIA § 3(b)–(c). Those amendments became effective eighteen months later on March 16, 2013. *Id.* at § 3(n). Because the ’227 patent claims priority to a provisional application filed before the effective date of the applicable AIA amendments (March 16, 2013), we refer to the pre-AIA versions of §§ 102 and 103 throughout this Decision.

⁷ Exhibit 1003 is a declaration by David G. Simpson, Ph.D., filed with the Petition.

B. Claim Construction

The challenged claims should be read in light of the Specification, as it would be interpreted by one of ordinary skill in the art. *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010). Thus, we generally give claim terms their ordinary and customary meaning. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) (“The ordinary and customary meaning is the meaning that the term would have to a person of ordinary skill in the art in question.” (internal quotation marks omitted)); *see also* 37 C.F.R. § 42.100(b) (stating that claims are construed in IPRs according to the same standard as used in federal court).

Although we did not construe expressly any claim term in our institution decision based on the arguments presented at the time, the parties now dispute the meaning of “major peaks” as that term appears in the challenged claims. In particular, Patent Owner argues that the ’227 patent provides an express and exclusive definition of “major peaks,” namely: “peaks higher than the average of the peaks in the result.” PO Resp. 7 (citing Ex. 1001, 13:28–29). Under this construction, Patent Owner argues that an FFT result cannot have major peaks unless it also has minor peaks. *See* PO Sur-Reply 7 (“To be clear: the claimed FFT result must have smaller/minor peaks; this is definitionally required to obtain an average height that is exceeded by ‘major peaks.’”).

Petitioner, on the other hand, disputes this lexicography-based construction in view of other evidence, both intrinsic and extrinsic. Pet. Reply 2–10. Given its importance to the overall patentability determination, it is necessary to resolve the parties’ claim construction dispute.

A patentee “may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition

of the term is clearly stated in the patent specification or file history.” *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) (citing *Hoechst Celanese Corp. v. BP Chemicals Ltd.*, 78 F.3d 1575, 1578 (Fed. Cir. 1996)); see *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995) (en banc) (“[A]ny special definition given to a word must be clearly defined in the specification.”), *aff’d*, 517 U.S. 370 (1996); *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002). “[T]he intrinsic evidence must ‘clearly set forth’ or ‘clearly redefine’ a claim term so as to put one reasonably skilled in the art on notice that the patentee intended to so redefine the claim term.” *Bell Atlantic Network Services, Inc. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001); see *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1370 (Fed. Cir. 2005).

Among the criteria to consider in whether the patentee acted as a lexicographer to define a claim term include (a) whether the patent specification included the statement in question under a section for “definitions,” (b) whether the term to be defined is set off in quotation marks, (c) whether the sentence uses the term “refer to,” which generally “conveys an intent for [that sentence] to be definitional,” and (d) whether there are other non-limiting terms (e.g., “for example,” or “include”) that contradict a definitional intent. *Alnylam Pharms., Inc. v. Moderna, Inc.*, 138 F.4th 1326, 1333 (Fed. Cir. 2025) (alteration in original).

At the outset, we agree with Patent Owner that the Specification purports to define “major peaks” in the following sentence: “The ‘major peaks’ herein refer to peaks higher than the average of the peaks in the result.” Ex. 1001, 13:28–29. We determine that this language satisfies at least two of the criteria set forth in *Alnylam*. Specifically, the sentence at

issue sets out “major peaks” in quotation marks, and then uses the term “refers to” to explain what qualifies as major peaks. That is not the end of the inquiry, however, as we find there is still some ambiguity as to whether the patentee intended to define “major peaks” so as to require so-called “minor peaks” in the claimed invention. *See Bell Atlantic*, 262 F.3d at 1268 (“[T]he intrinsic evidence must ‘clearly set forth’ or ‘clearly redefine’ a claim term so as to put one reasonably skilled in the art on notice that the patentee intended to so redefine the claim term.”).

Importantly, the Specification does not treat the existence of minor peaks as prerequisites for the existence of major peaks. Indeed, the Specification does not discuss “minor peaks” at all. *See generally* Ex. 1001. Likewise, none of the claims of the ’227 patent, whether challenged or unchallenged, recites “minor peaks” or any additional peaks beyond the disputed “major peaks.” *Id.* at 23:30–24:42. Nor does the Specification include an example of FFT analysis results in which the average of the peaks therein is calculated and those higher than the average are identified as major peaks.⁸

Rather, it appears, based on both the Specification as well as extrinsic evidence, that the named inventors of the ’227 patent assumed that an FFT analysis would *always* contain additional peaks that are not major peaks because it was thought impossible to manufacture a scaffold of perfectly

⁸ Indeed, as discussed *infra*, if such a calculation were applied to the FFT analysis result illustrated in Figure 8B, it would indicate that Figure 8B includes two major peaks at about 90° and 270° (i.e., about 180° apart), yet the ’227 patent states that Figure 8B relates to random fibers. *See* Ex. 1001, 2:12 (stating “Figure 8B depicts an FFT analysis of a control sample” of randomly oriented fibers); Ex. 2015 ¶51 (“Figure 8B as shown [sic] a control sample, e.g., with random fibers.”).

aligned fibers. For example, at oral argument, counsel for Patent Owner stated the following in response to questioning from the Board:

JUDGE KENNEDY: Counsel, this is Judge Kennedy. I have a quick question for you. So given your apparent position that the claim requires there to be minor peaks, is it also your position that the claim excludes a perfectly aligned scaffold?

MS. WIEKER: So the claim is directed to a real-world manufactured scaffold. For example, we've got this slide up here, and I'll direct you to Slide 9, as you see in Figure 8A [of the '227 patent]. The claim is directed to a real-world scaffold that has a principal axis of alignment that's represented by major peaks and additional axes of alignment reflected by minor peaks. And you can see that in the SEM image that's in the upper left of the slide.

So for example, the Ayres spaghetti strand example, that is perfectly aligned fibers, but it does not produce this FFT result because it does not have the major and minor peaks that are definitionally required.

JUDGE KENNEDY: So your claim, whether you want to call it a real-world scaffold or a slightly misaligned scaffold, your claim would require there to be at least some misalignment?

MS. WIEKER: Some minor peaks, yes. And as we just discussed, the peaks reflect fiber alignment, so it's going to be an additional or secondary axis of alignment.

Tr. 45:10–46:6; *see also* PO Sur-Reply 7–8 (Patent Owner's proposal for requiring minor peaks "reflects real-world scaffolds where 'high frequency signals' that 'reflect fiber alignment' are plotted as 'prominent or "major" peaks,' and where 'fibers that present additional orientations' are plotted as 'smaller or minor peaks.'"). This is consistent with Figure 8A of the '227 patent, which "depicts exemplary FFT analysis results of the [electrospun] fibers described" in the patent. Ex. 1001, 2:10–11. Figure 8A is reproduced below.

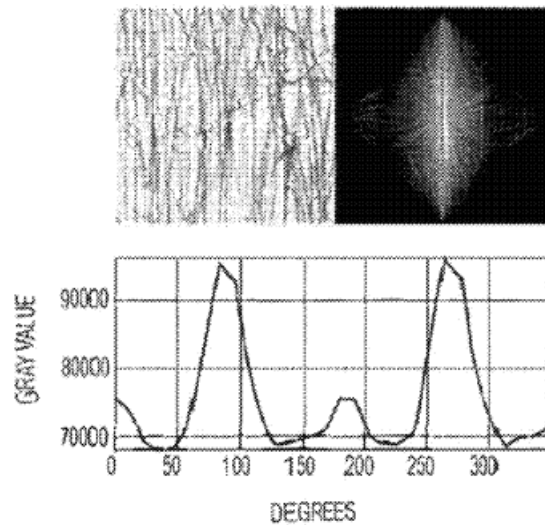


FIG. 8A

Ex. 1001, Fig. 8A. Figure 8A, reproduced above, includes three images. The top left image shows a SEM image of electrospun fibers. *Id.* at 21:25–45. As can be seen in the image, the fibers are predominantly aligned in a vertical orientation but several fibers are not so aligned. Consistent with some misalignment, the 2-dimensional FFT plot (bottom image) of the Fourier spectrum (top right) includes, not only major peaks at about 90° and 270°, but also smaller peaks at about 0° and 180°.

During continued questioning from the Board, counsel for Patent Owner implicitly argued that the challenged claims require some misalignment because they require minor peaks.

JUDGE KENNEDY: Given your specification[']s focus on alignment, is there any statement in the specification that makes clear that some misalignment is actually required, or you just have to read that into the definition of major peaks?

MS. WIEKER: So here, the patentee certainly could have claimed aligned fibers had they intended that to cover their invention, but what they did was elect to provide a specific definition that requires an FFT result with major peaks and define those major peaks as higher than an average. And there's no way

to understand that clear definition except from its requirement that there be minor peaks that are exceeded.

Tr. 46:7–17.

We are not satisfied by the purported distinction Patent Owner attempts to delineate. As discussed above, the '227 patent never discusses “minor peaks,” let alone as a requirement of the claimed invention.

The term “major peaks” must be read in light of the entire Specification. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (“the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification”). Here, the Specification repeatedly emphasizes that the disclosed invention relates to aligned fibers. *See, e.g.*, Ex. 1001, code (54) (“ALIGNED FIBER AND METHOD OF USE THEREOF”), code (57) (“A scaffold comprising an aligned fiber.”), 1:18–19 (“The invention relates to an aligned fiber and method of use thereof.”), 1:23–24 (“The invention relates to a scaffold comprising an aligned fiber.”). The Specification does not state, or even suggest, that the claimed invention is limited to a scaffold of *merely predominantly* aligned fibers. In other words, the Specification does not state that the claimed invention is limited to scaffolds that have *some* misalignment and/or secondary alignment.

We acknowledge that the Specification also describes “a scaffold comprising one or more electrospun fibers wherein a fast Fourier transform (FFT) analysis result of the fibers have adjacent major peaks with about 180° apart from each other.” *Id.* at code (57); *see also id.* at 1:25–28 (“In some embodiments, wherein [sic] a fast Fourier transform (FFT) analysis result of the fibers have adjacent major peaks with about 180° apart from

each other.”). However, the Specification explains that FFT is a tool for measuring alignment of the fibers. *Id.* at 13:38–39 (“Alignment of the fibers in the scaffold may be measured by a fast Fourier transform (FFT) analysis.”). This is not to suggest that we ignore the claim language reciting “wherein a result of a fast Fourier transform (FFT) analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other,” as recited in claim 1 and as nearly identically recited in claim 7. We give that language full weight, but we will not interpret the term “major peaks” so as to rewrite the language as requiring both minor peaks and major peaks in the FFT analysis result.

Although the Specification draws a clear distinction between random fibers (Fig. 8B) and aligned fibers (Fig. 8A), the Specification does *not* draw any distinction *between mostly aligned fibers and uniformly aligned fibers*. We cannot uncritically accept Patent Owner’s purported definition of “major peaks” so as to construe the claims to require so-called “minor peaks” that the claims do not affirmatively recite and which the Specification does not describe. *See Renishaw PLC v. Marposs Societa’ per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998) (“[A] claim must be read in view of the specification of which it is a part.”). This is especially true given the ’227 patent’s focus on creating “a scaffold comprising an aligned fiber,” whereas so-called “minor peaks” would be an indication of non-uniform alignment. Tr. 45:10–46:6; *cf. Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1383 (Fed. Cir. 2009) (Lourie, J., dissenting) (“This case illustrates the unusual situation in which a purported definition of a claim term in the written description is totally negated by the remainder of the text of the

patent. Martek’s attempt at lexicography does not conform to the way in which it otherwise describes its invention.”).⁹

Furthermore, adopting Patent Owner’s purported definition of “major peaks” would be inconsistent with the Specification’s description of Figure 8B as “depict[ing] an FFT analysis of a control sample” of randomly oriented fibers. Ex. 1001, 2:12; *see also* Ex. 2015 ¶51 (“Figure 8B as shown [sic] a control sample, e.g., with random fibers.”); PO Resp. 5 (stating that Figure 8B shows “non-aligned fibers”). Figure 8B again is reproduced below.

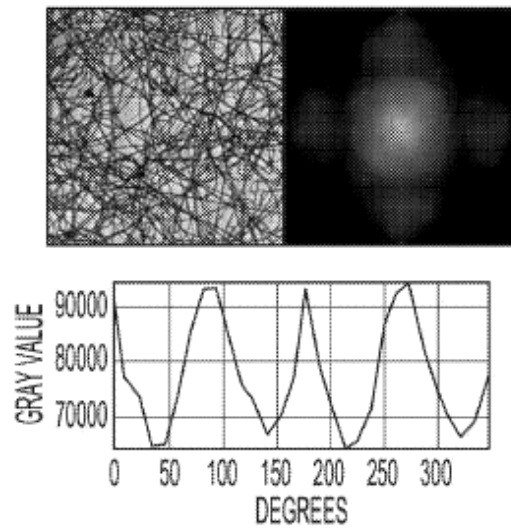


FIG. 8B

⁹ As we note above, the cited language in *Martek Biosciences* comes from a dissenting opinion. To be clear, the majority opinion in that case does not support Patent Owner’s position here. In *Martek Biosciences*, the majority enforced lexicography that resulted in a broader, not narrower, claim scope than that being proposed by the adversary and, importantly, it did not require the addition of an unstated limitation. *See* 579 F.3d at 1382 (“The proper construction for the claim term ‘animal’ is the one explicitly provided by the patentee [in the patent]: ‘any organism belonging to the kingdom Animalia,’ which includes humans.”). Here, Patent Owner asks us to narrow the claim scope by incorporating an unstated limitation, the presence of minor peaks.

Ex. 1001, Fig. 8B. Figure 8B, reproduced above, includes three images. As pointed out by Petitioner, under Patent Owner’s purported definition of “major peaks,” the FFT analysis depicted in the bottom image of Figure 8B has “adjacent major peaks with about 180° apart from each other” (i.e., at about 90° and 270°) as recited in claim 1. Pet. Reply 7–8; Ex. 1219 ¶¶8–19.¹⁰ This is so because those two peaks are higher than the average of the total of the three peaks that are shown (or four peaks if including one at 0°). But the Specification clearly disavows Figure 8B from the scope of the claims. Ex. 1001, 2:12.

In its Sur-Reply, Patent Owner attempts to obviate this potential conflict. In that regard, Patent Owner first argues that “Figure 8B depicts a ‘control’ sample of random fibers, *where no peaks exceed the average height (within conventional bounds of experimental error).*” PO Sur-Reply 4 (emphasis added). However, no citation is provided to support the italicized portion of the argument, which thus constitutes unpersuasive attorney argument. *See, e.g., Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043 (Fed. Cir. 2017) (“Attorney argument is not evidence.”).

Next, Patent Owner argues that “Ayres-2008, incorporated by reference [into the ’227 patent], likewise explains, ‘peaks of nearly uniform height’—like Figure 8B—indicate a random scaffold.” PO Sur-Reply 4–5 (citing Ex. 1010, 609; Ex. 2017, 88:7–15). It is true that Ayres 2008 is incorporated by reference into the ’227 patent. Ex. 1001, 13:39–46. It is also true that Ayres 2008 states: “Peaks of nearly uniform height are a hallmark of a scaffold composed of random elements.” Ex. 1010, 609.

¹⁰ Exhibit 1219 is a subsequent declaration by Dr. Simpson that Petitioner filed with its Reply.

However, this teaching by Ayres 2008 does not obviate the conflict in Patent Owner's position. To the contrary, it highlights the conflict, as it is further evidence that Figure 8B shows results obtained from "a scaffold composed of random elements." *Id.* Yet, if the purported definition of "major peaks" were adopted and applied literally, Figure 8B would be indicative of major peaks, which would be a clearly erroneous and nonsensical result.¹¹ Thus, Ayres 2008 does not support Patent Owner's construction.¹²

As discussed above, we agree with Patent Owner that the sentence it cites from the Specification of the '227 patent bears sufficient hallmarks of lexicography. However, the Specification nonetheless lacks any indication that so-called "minor peaks" are a necessary component of the claimed invention. "Although it is firmly settled that an applicant may act as a lexicographer in the specification, . . . the specification cannot support a definition that is contrary to the ordinary meaning of a claim term unless it communicates a deliberate and clear preference for this alternative definition." *Kumar v. Ovonic Battery Co.*, 351 F.3d 1364, 1368 (Fed. Cir. 2003). There is no indication that the patentee sought to require "minor peaks" within the scope of the claimed invention. Nor are we persuaded that a person of ordinary skill in the art would readily understand the scope of the term "major peaks" to require non-major peaks.

¹¹ Figure 8B does not contain "major peaks" despite clearly depicting two "peaks higher than the average of the [three or possibly four] peaks in the result" because none of the peaks is a reflection of fiber alignment.

¹² After presenting claim construction arguments based on Ayres 2008, Patent Owner confusingly states: "Finally, whether Ayres-2008 supports [Patent Owner's] construction *is irrelevant.*" PO Sur-Reply 6 (emphasis added).

We interpret the Specification's statement that "'major peaks' herein refer to peaks higher than the average of the peaks in the result" (Ex. 1001, 13:28–29) to be teaching a person of ordinary skill in the art how to identify or discern "major peaks," which indicate a principal axis of alignment, from any non-major peaks, which would be caused by something else.

We conclude that a person of ordinary skill in the art would consider "major peaks" as used in the '227 patent as referring to peaks that reflect the sole axis or primary axis of fiber alignment. *See, e.g., id.* at code (54) ("ALIGNED FIBER AND METHOD OF USE THEREOF"), code (57) ("A scaffold comprising an aligned fiber."), 1:18–19 ("The invention relates to an aligned fiber and method of use thereof."), 1:22–23 ("The invention relates to a scaffold comprising an aligned fiber."), 13:38–39 ("Alignment of the fibers in the scaffold may be measured by a fast Fourier transform (FFT) analysis."). This would certainly include peaks materially higher than the average of the peaks in the result, but it would not be limited to situations involving peaks of different heights or require so-called minor peaks. Based on the totality of the evidence before us, we do not construe the claims to require non-major peaks.

C. The Prior Art

1. Huang2 (Ex. 1005)

Chengyang Huang et al., *The involvement of integrin $\beta 1$ signaling in the migration and myofibroblastic differentiation of skin fibroblasts on anisotropic collagen-containing nanofibers*, 33 *Biomaterials* 1791–1800 (Feb. 2012) ("Huang2") is a journal article that was first published online on

December 2, 2011. Ex. 1005, 1791.¹³ Huang2 qualifies as prior art under pre-AIA 35 U.S.C. § 102(b). Pet. 21. Patent Owner does not dispute that Huang2 is available as prior art.

Huang2 studies collagen fibers used for tissue-engineered skin grafts. Ex. 1005, 1791. In particular, Huang2 compares aligned (anisotropic) fibers to non-aligned (isotropic) fibers¹⁴ with regard to their effect on the attachment and growths of normal human dermal fibroblasts (“NHDFs”). *Id.* To mimic the skin’s native extracellular matrix (“ECM”), Huang2 discusses creating scaffolds of electrospun collagen fibers. *Id.* Huang2 teaches that, when doing so, “either crosslinking or blending with other materials is necessary to obtain a stable scaffold.” *Id.* Huang2 states that, for the scaffolds that its researchers fabricated, blending with polycaprolactone (PCL) was used. *See id.* at 1792 (“Nanofibrous matrices of PCL and Collagen at a weight ratio of 3:1 were fabricated using electrospinning as previously described.”).

Huang2 characterizes both isotropic and anisotropic PCL/collagen blends in several ways, including by SEM and FFT analysis. With regard to FFT analysis, Huang 2 discloses:

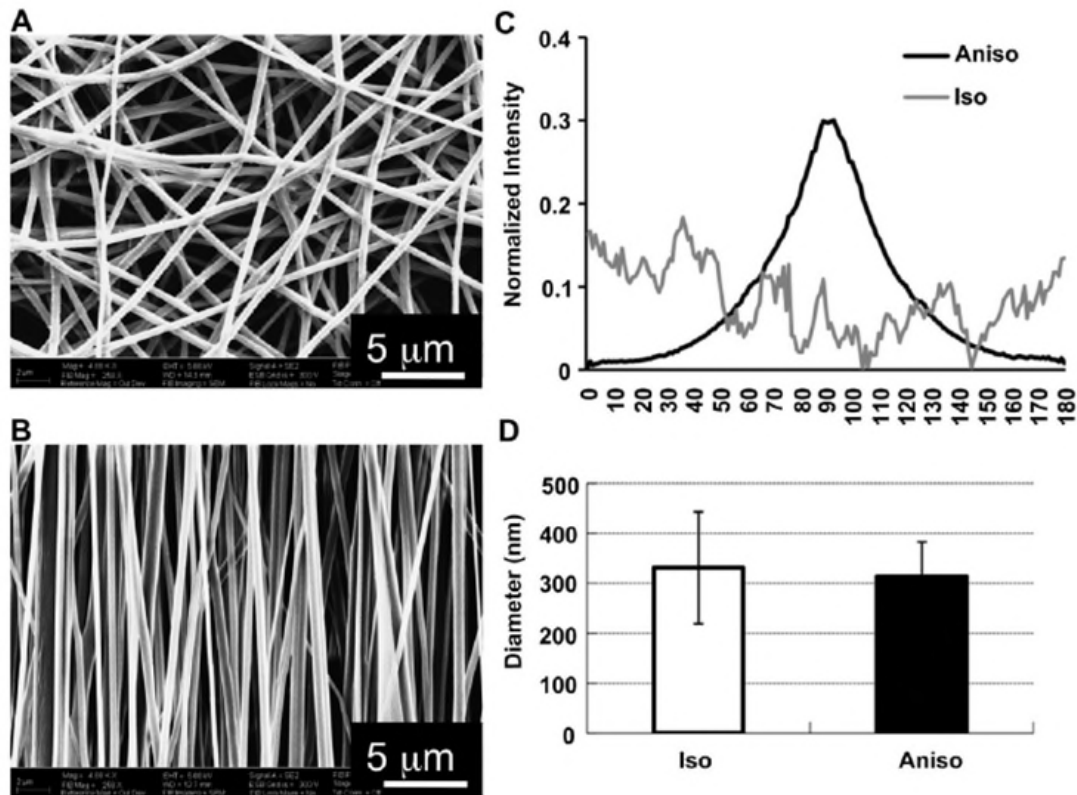
¹³ A different reference by Huang, identified as “Huang1” (Ex. 1008) in the Petition, was considered by the Examiner during prosecution of a parent application. *See* Pet. 17–19 (citing Ex. 1007, 210).

¹⁴ Isotropic fibers are randomly oriented, and anisotropic fibers are aligned. *See* Ex. 1005, 1792 (“To address this hypothesis together with the attempt to mechanistically understand fiber alignment-induced cell migration, normal human dermal fibroblasts (NHDFs) were seeded on collagen-containing PCL nanofibrous matrices with either isotropic nanofiber arrangement (*i.e.*, randomly collected nanofibers with no alignment, abbreviated as ‘*Iso*’) or anisotropic nanofiber arrangement (*i.e.*, collected nanofibers with alignment, abbreviated as ‘*Aniso*’).”).

The orientation of electrospun nanofibers was determined by using the ImageJ program (NIH) along with the Oval Profile Plot plugin [22¹⁵]. Briefly, representative SEM images of the electrospun fibers were cropped into a square covering as much of the image as possible (the images used were 905 x 905 pixels in size). These cropped images were then processed with a fast Fourier transform (FFT) and then a circular section of the image was made maximizing the amount selected (edges of the circle were tangent with the edges of the image). This selection then underwent a radial summation using the Oval Profile Plot plugin with 360 points such that the degree interval was 1°. The raw data were normalized to 0 and data from all sets were rescaled to an arbitrary range between 0 and 0.3. The final results were presented by plotting this arbitrary scale *versus* degrees, where the height of the peaks represents a greater degree of alignment at a given angle.

Ex. 1005, 1792. The results are shown in Figure 1, reproduced below:

¹⁵ Reference [22] in Huang2 refers to Chantal Ayres *et al.*, “*Modulation of anisotropy in electrospun tissue-engineering scaffolds: analysis of fiber alignment by the fast Fourier transform*” 27(32) BIOMATERIALS 5524–34 (2006) (“Ayres 2006,” Ex. 1013). *See* Ex. 1005, 1800. Although not relied upon to teach any particular claim limitations, Ayres 2006 and Ayres 2008 are discussed below given their relevance to Petitioner’s patentability challenges.



Ex. 1005, Fig. 1. Figure 1A (top left) shows a SEM image of an isotropic (random fibers) sample of a PCL/collagen nanofibrous matrix, whereas Figure 1B (bottom left) shows a SEM image of an anisotropic (aligned fibers) sample. *Id.* at 1793. Figure 1C (top right) shows the normalized intensity plots against the angle of acquisition for the isotropic and anisotropic samples obtained using FFT analysis. *Id.* Figure 1D (bottom right) shows the measured average fiber diameter of both matrices. *Id.*

Huang2's results showed that fibroblast-to-myofibroblast differentiation, important to the reconstruction of connective tissue during wound healing, was enhanced in the anisotropic PCL/collagen nanofibers due to the impact of the alignment on the integrin $\beta 1$ signaling pathway. *Id.* at 1797–99.

2. *Kuo (Ex. 1018)*

United States Patent Application Publication No. 2011/0293685 A1 (“Kuo”) was published on December 1, 2011. Ex. 1018, code (43). It qualifies as prior art under pre-AIA 35 U.S.C. § 102(b). Patent Owner does not dispute Kuo’s availability as prior art.

Kuo is titled “Scaffolds For Tissue Engineering And Regenerative Medicine” and discloses electrospun collagen/PCL scaffolds for “tissue repair” that are seeded with cells and formed into a desired shape to replace tissue including muscles, *ligaments, tendons, and nerves*, among others. *Id.* at codes (54), (57), ¶¶5, 52, 113. The scaffolds described in Kuo are created by electrospun micro or nano fibers with “fiber orientation that is random, *aligned*, or any combination thereof.” *Id.* ¶5 (emphasis added). Kuo proceeds to describe “methods and compositions using aligned nanofiber materials as scaffolds for engineering tendon or ligament tissues with stem/progenitor cells.” *Id.* ¶112. Kuo reports that its aligned nanofiber scaffolds “are seeded with cells and subsequently rolled into cylindrical form, to form structures e.g., that mimic that of fascicles of the muscle, tendon, nerve, or ligament.” *Id.* ¶34. For example, for tendon and ligament applications, Kuo explains that its “aligned nanofiber scaffold locally mimicked the native microstructure of tendon/ligament (aligned collagen fibrils), globally mimicked a fascicle or bundle in tendon/ligament tissue, and resulted in cell seeding throughout the construct.” *Id.* ¶112.

Kuo further notes that the fibers may be comprised of natural materials (including collagen), synthetic materials, or a combination of both natural and synthetic materials. *Id.* ¶¶5, 14. Kuo describes the cells that can seed the scaffold as “selected from the group consisting of stem cells, osteoblasts, myoblasts, neuroblasts, fibroblasts, glioblasts, germ cells

hepatocytes, chondrocytes, keratinocytes, smooth muscle cells, cardiac muscle cells, connective tissue cells, epithelial cells, endothelial cells, hormone-secreting cells, neurons, tenocytes, skeletal myocytes, and skeletal myoblasts.” *Id.* ¶16; *see also id.* ¶¶58–66.

3. *Lee (Ex. 1011)*

United States Patent Application Publication No. 2010/0331980 A1 (“Lee”) was published on December 30, 2010. Ex. 1011, code (43). It qualifies as prior art under Pre-AIA 35 U.S.C. § 102(b). Patent Owner does not dispute Lee’s availability as prior art.

Lee is generally directed to an aligned scaffolding system for skeletal muscle regeneration. *Id.* at (54). Lee teaches that the reconstruction of skeletal muscle tissue lost, for example, due to a traumatic injury is difficult because of “the lack of available functional muscle tissue substitutes.” *Id.* ¶3. To solve this problem, Lee describes engineered muscle tissue, including “a biodegradable scaffold comprising a plurality of fibers oriented along a longitudinal axis of the fibers” and “methods of forming a biodegradable scaffold, including the steps of: electrospinning a solution comprising a biodegradable scaffold material onto a grounded mandrel to form a plurality of fibers oriented along a longitudinal axis; and crosslinking said fibers to form the scaffold.” *Id.* ¶¶5–6. Lee explains that its “[s]caffold” refers to an array of natural or synthetic matrix molecules to which cells or fibers can attach,” which it further explains may include various components and molecules. *Id.* ¶44.

Lee describes using fibers for the scaffold that are natural, such as collagen, or synthetic, such as PCL, or blends of natural and synthetic fibers between 2:1 and 1:2 by weight. *Id.* ¶5. Lee also describes obtaining

electrospun nanofiber meshes¹⁶ “using a blend of PCL and collagen with a ratio of 1:1 in weight.” *Id.* ¶¶62–63. Lee explains that “PCL-collagen composite scaffolds according to some embodiments have preferable biomechanical properties, e.g., yield tensile strength, elasticity and compliance.” *Id.* ¶52. Lee teaches that when PCL and collagen are used together, there is “improved biocompatibility, mechanical properties, and processability,” and further explains that “in some embodiments the biomechanical properties of PCL-collagen scaffolds are similar to that of native tissue.” *Id.*

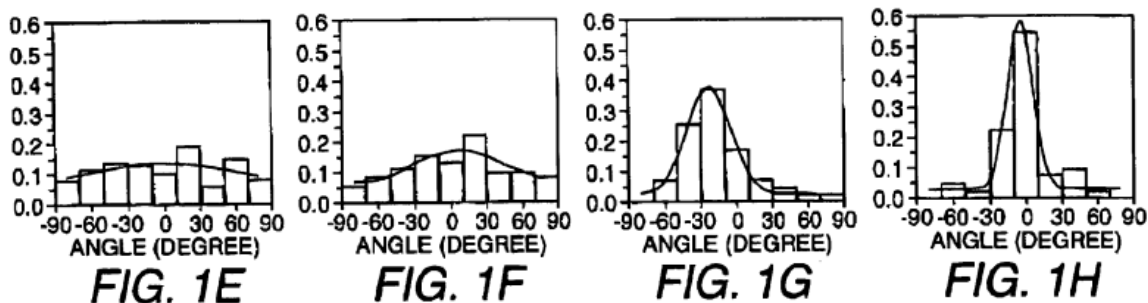
Further, Lee teaches fabricating “nanofiber meshes that are aligned in a unidirectional manner to facilitate myotube formation” in order to approximate skeletal muscle. *Id.* ¶90. Lee explains that previous studies demonstrated that “aligned nanofibrous structures can be obtained using a variety of collecting mandrel systems, including rotating drum.” *Id.* ¶91. Lee discovered that “[f]iber alignment had a profound effect on the mechanical properties of electrospun PCL/collagen nanofiber meshes,” including increased tensile strength for the aligned nanofiber meshes. *Id.* ¶81.

Lee explains that the aligned fibers aided in cell growth—“[t]he myotubes that formed on the oriented nanofiber meshes showed unidirectionally organized myotubes that are consistently aligned along the longitudinal axis of nanofibers, which is in contrast to the randomly oriented nanofiber meshes (FIGS. 5c, f).” *Id.* ¶84. While the “myotubes formed on

¹⁶ Lee uses the terms “scaffold,” “mesh,” and “matrix” interchangeably. *See* Ex. 1011 ¶45 (“A ‘biodegradable scaffold,’ ‘biodegradable mesh’ or ‘biodegradable matrix’ is a scaffold having materials capable of being degraded and/or absorbed in a subject’s body.”).

the randomly oriented nanofiber meshes . . . did not show a global cellular organization,” Lee states that the “myotubes on the aligned nanofiber meshes organized within close proximity to the direction of the nanofiber direction and formed globally aligned myotubes (FIG. 6d).” *Id.* ¶85.

Lee obtained SEM images and plotted histograms of fiber angles for fibers that were electrospun at different rates of rotation. *Id.* ¶11. Figures 1E–1H of Lee are reproduced below:



The figures above show normalized histograms of fiber angles obtained at different rates of rotation, ranging from “static” (Fig 1E on the left) to 2350 rpm (Fig. 1H on the right). *Id.* ¶11. As shown above, a distinct peak occurs in the histogram for fibers obtained at higher rates of rotation, which reflects the fiber orientation at that angle.

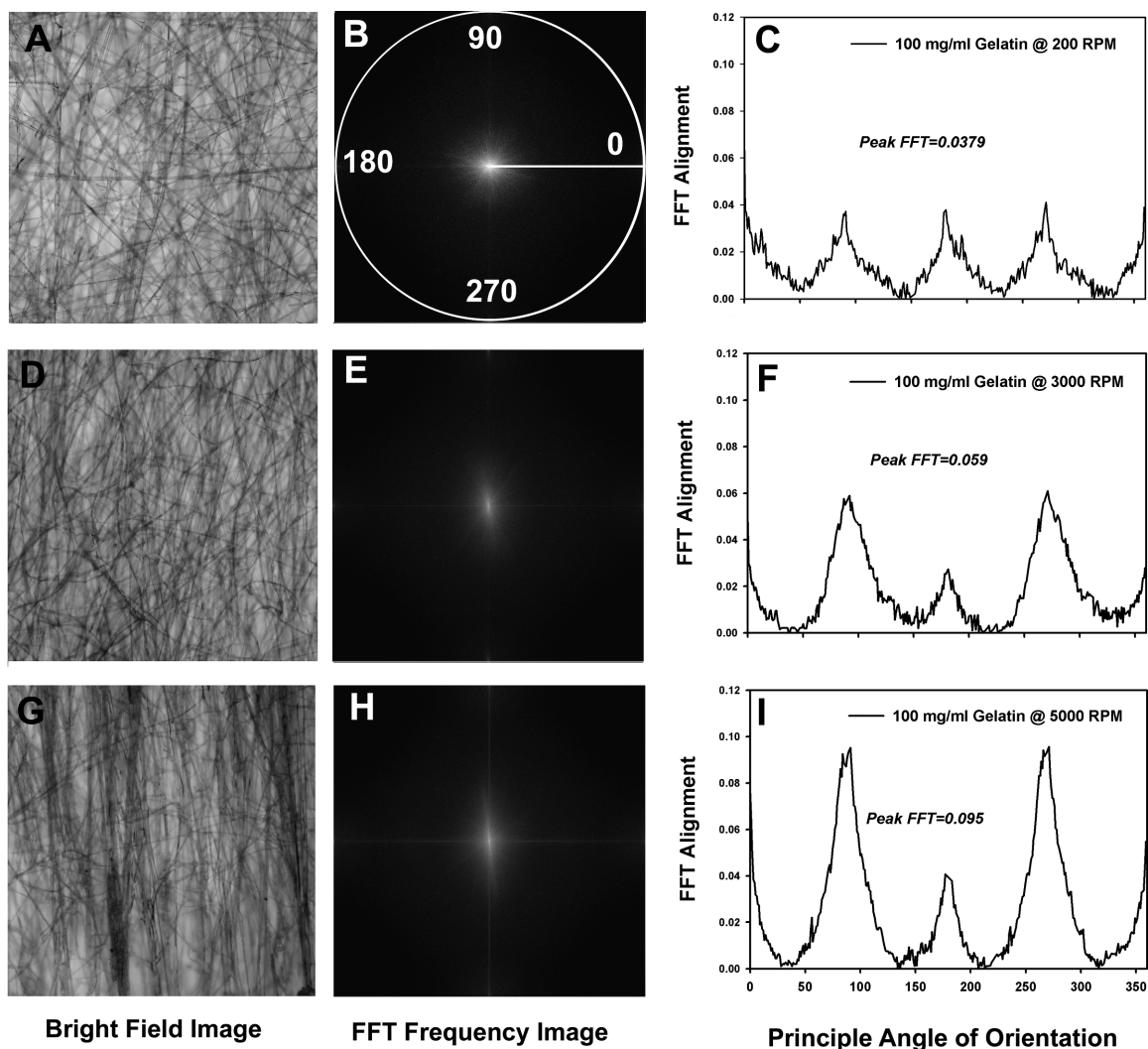
Lee concludes that the “[a]ligned nanofibers greatly influenced muscle cell organization and enhanced myotube formation,” and that “myotubes formed on the aligned nanofiber meshes were highly organized and were significantly longer than that of the myotubes on the randomly oriented meshes.” *Id.* ¶94. “These findings indicate that the electrospun PCL/collagen nanofiber meshes are able to guide and orient skeletal muscle cells into organized structures that mimic native tissues.” *Id.*

4. *Ayres 2008 (Ex. 1010)*

Ayres 2008 is an article published in JOURNAL OF BIOMATERIALS SCIENCE, POLYMER EDITION in 2008 and was later published online on April 2, 2012. Ex. 1010, 604. As noted above, Ayres 2008 was incorporated by reference into the '227 patent. Ex. 1001, 13:39–46. Petitioner's declarant, Dr. Simpson, is one of the named authors of Ayres 2008. Patent Owner does not dispute that Ayres 2008 qualifies as prior art.

Ayres 2008 describes a method of using two-dimensional fast Fourier transform (2D FFT) to measure fiber alignment in electrospun materials. Ex. 1010, 604. As explained in Ayres 2008, “[a] data image of an electrospun scaffold is composed of pixels that depict the spatial organization of the constituent fibers.” *Id.* at Abstr. “The 2D FFT function converts this spatial information into a mathematically defined frequency domain that maps the rate at which pixel intensities change across the original data image,” which thereby provides “quantitative information concerning the orientation of objects in a data image.” *Id.*; *see also id.* at 608. ImageJ software (obtained from the NIH) supported by an oval profile plug-in was used to conduct the 2D FFT analysis. *Id.* at 607.

Figure 1 of Ayres 2008 is reproduced below:



Ex. 1010, Fig. 1. Figures 1A, 1D, and 1G (left column) show brightfield images of representative electrospun scaffolds composed of fibers with varying degrees of alignment. Figures 1B, 1E, and 1H (middle column) show the ImageJ-generated “frequency plots,” while Figures 1C, 1F, and 1I on the right show the “2D FFT alignment plots” for the corresponding brightfield images.

As explained in Ayres 2008, “[w]hen an image of random fibers is processed by 2D FFT, the resulting frequency plot contains a cluster of white pixels that are concentrated in a symmetrical, circular pattern around the origin (Fig. 1B).” *Id.* at 609. On the other hand, the frequency plot for

an image of aligned fibers will contain pixels “concentrated along a specific axis” (Figs. 1E, 1H). *Id.* at 610. After rotating the frequency plot by 90°, the intensities of the pixels are summed along the radius for each angle of a circular projection (0–360°) placed on the image using the ImageJ software. *Id.* at 609. The summed pixel intensities are then plotted against the corresponding angle to produce the 2D FFT alignment plot. Although Figures 1C, 1F, and 1I show the alignment data for the full 360° projection, Ayres 2008 notes that “[t]ypically, the data from this analysis is reported for 0 to 180°” because “the frequency plot is symmetric so a complete summation from 0 to 360° is not technically necessary.” *Id.*

As depicted in Figure 1C, “[t]he 2D FFT alignment plot of a random matrix will exhibit 4 peaks that occur every 90°.” *Id.* By contrast, “[t]he 2D FFT alignment plots generated from sample scaffolds containing aligned elements exhibit asymmetrical peaks, two larger peaks at 90 and 270° and two smaller peaks at 0 and 360° (Fig. 1F and I).” *Id.* at 610. Ayres 2008 explains that “[t]he degree of alignment present in the original data image is reflected by the height and overall shape of the most prominent peaks present in the alignment plot.” *Id.*

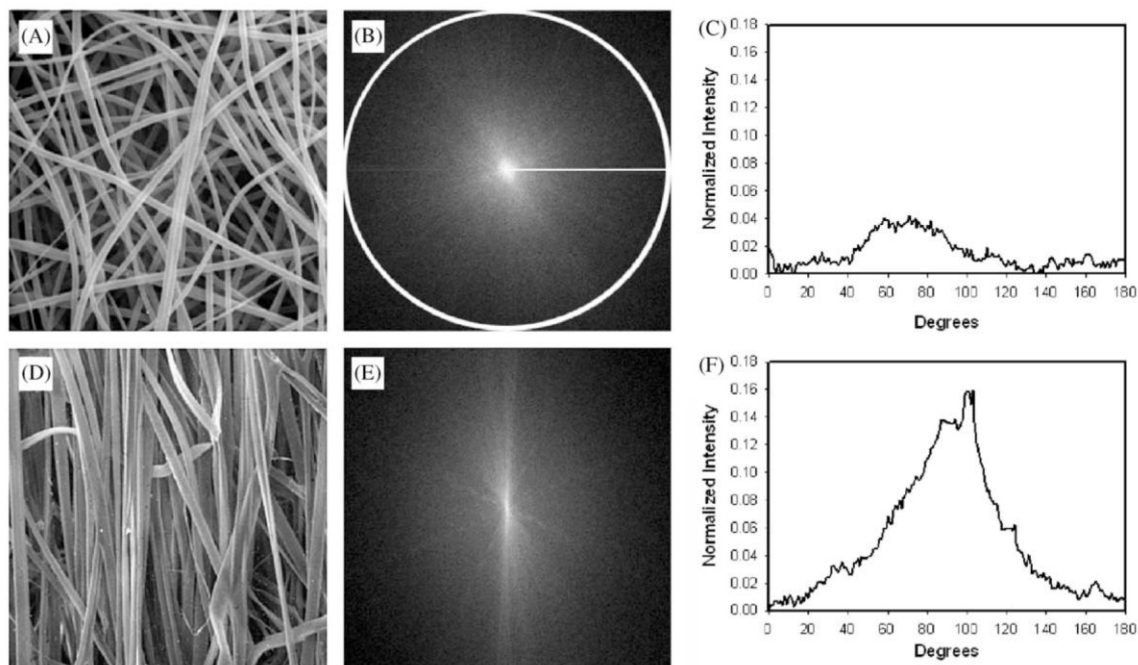
5. *Ayres 2006 (Ex. 1013)*

Ayres 2006 is an article published in *BIOMATERIALS* in 2006 and was later published online at PubMed Central in 2010. Ex. 1013, 1. It names several of the same authors as Ayres 2008, including Petitioner’s declarant, Dr. Simpson. As noted above, Huang² cites Ayres 2006 as the source for the FFT methodology used therein. Ex. 1005, 1800. Patent Owner does not dispute that Ayres 2006 qualifies as prior art.

Ayres 2006 describes the use of FFT in the measurement of anisotropy in electrospun scaffolds of gelatin. Ex. 1013, 1. Ayres 2006 notes that, “[b]y using FFT to assign relative alignment values to an electrospun matrix it is possible to systematically evaluate how different processing variables impact the structure and material properties of a scaffold.” *Id.*

Ayres 2006 describes an FFT process, similar to that of Ayres 2008, for quantifying the degree of fiber alignment. As explained in Ayres 2006, “[t]he FFT function converts information present in an original data image from ‘real’ space into mathematically defined ‘frequency’ space,” with “[t]he resulting FFT output image contain[ing] grayscale pixels . . . distributed in a pattern that reflects the degree of fiber alignment present in the original data image.” *Id.* at 3. According to Ayres 2006, “[a] graphical depiction of the FFT frequency distribution can be generated by placing a circular projection on the FFT output image and conducting a radial summation of the pixel intensities for each degree between 0° and 360°, in 1° increments.” *Id.* at 4. Once these summations are obtained, the pixel intensities were plotted between 0° and 180°. *Id.* Ayres 2006 notes that, because “the FFT is symmetric about the horizontal axis[, . . .] a pixel summation to 360° is unnecessary.” *Id.*

Using this methodology, Ayres 2006 presents the results of an FFT analysis for a subjectively judged “random” matrix and an “aligned” matrix in Figure 1, which is reproduced below.



Ex. 1013, 12. Figure 1, reproduced above, shows two rows of three images. The upper row of images depicts, from left to right, a SEM image of a *random matrix* (Fig. 1A), the corresponding FFT output image (Fig. 1B), and the resulting pixel intensity plot (Fig. 1C). *Id.* The lower row of images depicts, from left to right, a SEM image of an *aligned matrix* (Fig. 1D), the corresponding FFT output image (Fig. 1E), and the resulting pixel intensity plot (Fig. 1F). *Id.* As shown above, the FFT output image for the aligned matrix contains pixels distributed in a “non-random, elliptical distribution” compared to the “symmetrical, circular shape” for the FFT output image of the random matrix. *Id.* at 3–4. “This distribution occurs because the pixel intensities are preferentially distributed with a specific orientation.” *Id.* at 4. The pixel intensity plot for the aligned matrix shows a distinct peak around 90°, with the height and overall shape of the peak reflecting the degree of alignment. *Id.*

D. Ground 1: Obviousness over Huang2 and Kuo

In Ground 1, Petitioner contends that claims 1–6 would have been obvious over Huang2 and Kuo. Pet. 28–45. As explained below, we find that Petitioner has proven this contention by a preponderance of evidence as to claims 1, 4, 5, and 6, but not as to claims 2 and 3.

1. Independent Claim 1

Independent claim 1 recites “[a] method of treating a tissue defect in a subject comprising implanting at the tissue defect a scaffold.” Ex. 1001, 23:29–31. With regard to this limitation, Petitioner argues that Huang2’s “scaffolds are designed to treat a tissue defect in a subject, i.e., a wound in the skin.” Pet. 31 (citing Ex. 1005, 1791). Patent Owner does not dispute that Huang2 discloses a method of treating a tissue defect in a subject comprising implanting at the tissue defect a scaffold as argued by Petitioner. PO Resp. 13–39. We are persuaded that Huang2 discloses this claim element.

Independent claim 1 further recites that the “scaffold compris[es] crosslinked fibers comprising collagen.” Ex. 1001, 23:31–32. With regard to this limitation, Petitioner points to Huang2’s teaching of nanofibrous matrices made from a blend of PCL and collagen, and that “crosslinking” can be used to “obtain a stable scaffold.” Pet. 33 (citing Ex. 1005, 1791–92). Petitioner further points to Kuo’s teaching of an electrospun blend of PCL:collagen type I. With regard to the crosslinking requirement, Petitioner points to Kuo’s incorporation by reference of Lorenz Meinel, *et al.*, *Engineering Cartilage-Like Tissue Using Human Mesenchymal Stem Cells and Silk Protein Scaffolds*, 88(3) BIOTECHNOL. BIOENG. (2004) 88:379–391 (“Meinel,” Ex. 1023), regarding preparation of the scaffold from electrospun

fibers. Pet. 33–34 (citing Ex. 1018 ¶40). As noted by Petitioner, Meinel teaches that crosslinking can decrease the rate of collagen degradation by two orders of magnitude. *Id.* at 34 (citing Ex. 1023, 380–81, 390).

Petitioner contends that “a skilled artisan would have been motivated with a reasonable expectation of success to utilize Huang2’s aligned fibers to create a scaffold that can treat a tissue defect, and would have been motivated to improve the stability of collagen fibers by chemically crosslinking, as taught by both Huang2 and Kuo.” *Id.*

We focus our analysis on the teachings of Huang2 (and not Kuo) because we find Huang2’s teachings regarding crosslinking sufficient to support Petitioner’s challenge as we explain below.

Patent Owner concedes that Huang2 “discloses crosslinking as one possible way to obtain a stable scaffold,” but argues that Huang2 “*does not employ crosslinking*” and instead achieves scaffold stability by “blend[ing] polycaprolactone (PCL) with collagen.” PO Resp. 13 (citing Ex. 1005, 1791–92). Patent Owner further argues that “[t]he Petition does not suggest—let alone demonstrate—that Huang2’s blended fibers are insufficiently stable such that a POSITA would additionally crosslink those fibers.” *Id.* Patent Owner cites Dr. Mikos’s testimony that crosslinking and blending “are alternative ways to achieve stability.” *Id.* (citing Ex. 2015 ¶64).

Petitioner replies that “the ’227 patent [itself] teaches that crosslinking was a ‘conventional’ technique that therefore must be within the level of skill of a POSA.” Pet. Reply 20 (quoting Ex. 1001, 12:49–58). Petitioner continues, “[c]onsistent with [it] being a conventional technique, Huang2 teaches crosslinking as one method to improve stability of its scaffold, which is legally sufficient to render the element obvious.” *Id.*

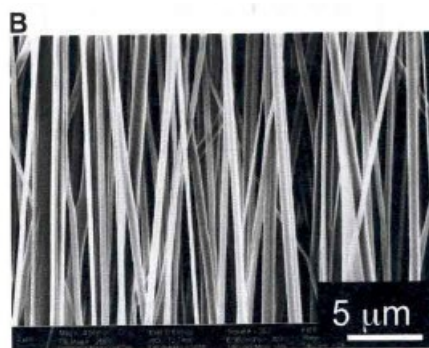
In its Sur-Reply, Patent Owner argues “[i]t is insufficient to simply allege that Huang2’s fibers *could have been* crosslinked” and asserts that “Petitioner does not allege that Huang2’s blended fibers are insufficiently stable or would have benefited from crosslinking in another way.” PO Sur-Reply 12.

Petitioner has the better position. Huang2 teaches crosslinking and provides a reason for doing so (stability). In particular, Huang2 states: “To better mimic skin ECM, electrospun collagen fibers have been fabricated, however, the rapid degradation and poor mechanical properties determine that either *crosslinking* or combination with other materials is necessary *to obtain a stable scaffold*.” Ex. 1005, 1791 (emphasis added). It is true that, in describing work actually carried out, Huang2 states that blending with PCL was performed and does not mention crosslinking. *See id.* at 1792 (“Nanofibrous matrices of PCL and Collagen at a weight ratio of 3:1 were fabricated using electrospinning as previously described.”). However, the prior art – here, Huang2 – is not limited to that which it describes having created. *See In re Mills*, 470 F.2d 649, 651 (C.C.P.A. 1972) (“a reference is not limited to the disclosure of specific working examples”); *see also In re Lemelson*, 397 F.2d 1006, 1009 (CCPA 1968) (“The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain.”); *In re Fritch*, 972 F.2d 1260, 1264 (Fed. Cir. 1992) (“It is well settled that a prior art reference is relevant for all that it teaches to those of ordinary skill in the art.”). Huang2 teaches two stabilization methods when using collagen in scaffolds. Huang2 states that one or the other “is necessary to obtain a stable scaffold” (when using collagen), but it does not preclude or teach away from using

either method or even from using both methods in combination. Indeed, the Patent Owner-cited testimony of Dr. Mikos is not as definitive as Patent Owner suggests; Dr. Mikos's testimony is that a person of ordinary skill in the art "*typically* would not have done both." Ex. 2015 ¶64 (emphasis added).

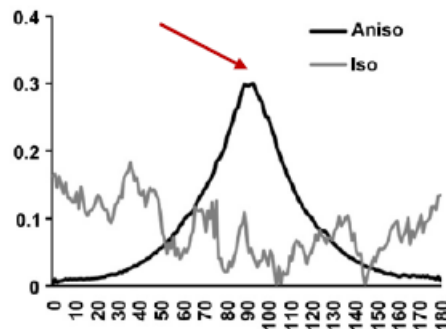
The bottom line is that Huang2 teaches the person of ordinary skill in the art two ways to stabilize scaffolds/matrices comprised of collagen, provides a reason for doing so (stability), and does not teach away from using both. We are persuaded that a "scaffold comprising crosslinked fibers comprising collagen" would have been obvious in view of the cited teachings of Huang2.

Independent claim 1 further recites "wherein a result of a fast Fourier transform (FFT) analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other." Ex. 1001, 23:32–35. With regard to this limitation, Petitioner argues that "Huang2 describes PCL/collagen nanofibers that are highly aligned with major peaks that are about 180° apart." Pet. 35. Huang2 Figure 1B is reproduced below.



Ex. 1005, Fig. 1B. Figure 1B, reproduced above, shows a SEM image of an "anisotropic" (aligned) sample. *Id.* at 1793. Patent Owner does not dispute that Huang2 discloses a PCL/collagen nanofibrous matrix of aligned fibers. PO Resp. 11.

Petitioner next points to Huang2's statement that, "[t]o better analyze the fiber alignment, FFT analysis was performed on [Huang2]'s SEM images . . . to characterize the anisotropy [(i.e., alignment)] and assign a numerical value to fiber orientation." Ex. 1005, 1794 (cited at Pet. 35–36). The FFT results of both the aligned and unaligned fibers are plotted in Figure 1C, which is reproduced below, with Petitioner's annotation.



Pet. 36 (annotating Ex. 1005, Fig. 1C). Figure 1C, reproduced above as annotated by Petitioner, shows the normalized intensity plots against the angle of acquisition, from 0° through 180°, for the aligned (Aniso) and unaligned (Iso) samples obtained using FFT analysis. Ex. 1005, 1793.

Petitioner argues that, for the aligned sample, a major peak occurs at about 90° as identified by Petitioner's annotation (red arrow). Pet. 36. As support, Petitioner directs us to Huang2's explicit description of what the peak indicates, namely that "[t]he narrow peak of the normalized intensity values in anisotropic [aligned] matrices (Figure 1C) indicated that *PCL/Coll nanofibers aligned along a single axis* (Fig. 1B)." *Id.* at 36–37 (alteration in original) (quoting Ex. 1005, 1794). Patent Owner disputes that the illustrated peak is a major peak solely based on the lack of any lesser peaks. *See* PO Resp. 17 ("[T]he height of the sole peak is *identical to*—not higher than—the average height of the peaks in the result."). As discussed above,

however, we do not construe “major peaks” as requiring the existence of non-major peaks.

We find that the illustrated peak in the Aniso plot of the FFT analysis results (Figure 1C) is a major peak within the meaning of the claim. The evidence in support of this finding is overwhelming. First, the term “Aniso” as used in Huang2 refers to fibers “with alignment.” Ex. 1005, 1792.

Huang2 describes fabricating such matrices of aligned fibers with electrospinning, the same method used to impart alignment in the ’227 patent. *Id.* at 1791–92. Huang2 visually confirms that the fibers in fact are aligned via scanning electron microscopy. *Id.* at Fig. 1B. Further, Huang2 explicitly states that the peak illustrated in the Aniso plot of the FFT analysis results (Figure 1C) is caused by the fact that the “PCL/Coll nanofibers aligned along a single axis (Fig. 1B).” *Id.* at 1794. This is precisely what the ’227 patent states is to be expected. The ’227 patent discloses that electrospinning may yield aligned fibers and images of aligned fibers will yield FFT results with major peaks. Ex. 1001, 2:42–44, 5:4–18, 13:38–49.

Additionally, Huang2 itself considers the peak illustrated in the Aniso plot of the FFT analysis to be *significant*, stating: “In contrast [to the Aniso plot], the lack of a significant peak for the fibers collected on a stationary surface [(i.e., without electrospinning)] demonstrated no preferred fiber orientation in the isotropic matrices” (i.e., the Iso plot). Ex. 1005, 1794. Indeed, the asserted major peak in the Aniso plot shown in Huang2’s Figure 1C is higher than any other data point on the plot.

For these reasons, we find the peak to be a major peak.¹⁷

Petitioner acknowledges that Figure 1C only reports its results through 180°, but contends that “Huang2’s FFT analysis would necessarily show a second major peak at around 270° (which is 180° from the 90° peak) if the scale were extended to 0°–360°.” Pet. 37 (citing Ex. 1010, 609). Petitioner’s evidence on this point is strong. *See* Ex. 1010, 609 (“Typically, the data from this [FFT] analysis is reported for 0 to 180°; the frequency plot is symmetric so a complete summation from 0 to 360° is not technically necessary.”); Ex. 1013, 4 (“the FFT is symmetric about the horizontal axis so a pixel summation to 360° is unnecessary”) (cited at Pet. 9). Indeed, Patent Owner does not dispute that a second and identical peak would exist around 270° if the Aniso plot shown in Huang2’s Figure 1C were extended. *See, e.g.*, PO Sur-Reply 12 (arguing that neither peak is a major peak but not disputing that the second peak would occur). These two peaks – at about 90° and 270° – are “about 180° apart from each other,” as recited in claim 1. We are persuaded that Huang2 discloses this claim element.

Claim 1 further recites “applying the scaffold to the tissue defect to repair a tendon, a ligament or a nerve defect.” Ex. 1001, 23:36–37. With regard to this limitation, Petitioner first points out that Huang2 discusses using its scaffolds of aligned fibers comprising collagen to repair a tissue injury generally. Pet. 39. Indeed, Huang2 discusses skin injury applications. *See, e.g.*, Ex. 1005, Abstr. (discussing “[u]tilization of nanofibrous matrices for skin wound repair”). Petitioner, however, does not

¹⁷ Although we reject Patent Owner’s construction of “major peaks,” Patent Owner argues that it “reflects real-world scaffolds.” PO Sur-Reply 7; *see also* Tr. 45:10–20. There is no dispute that Huang2’s scaffold that produced the “Aniso” plot in the figure is a real-world scaffold.

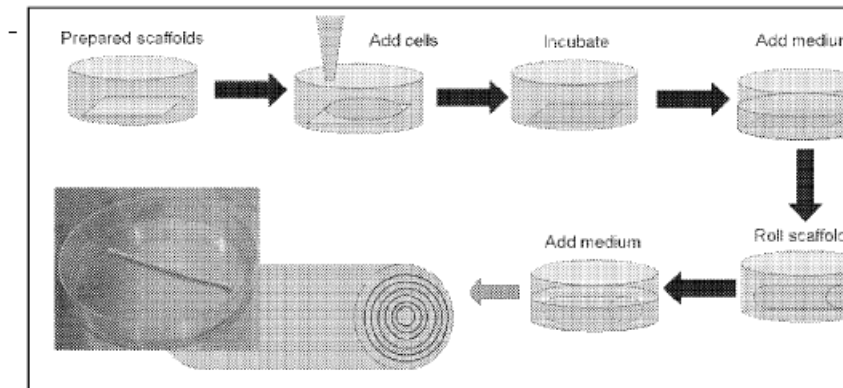
argue that Huang2 teaches tendon, ligament, or nerve injury applications in particular. Pet. 39. Instead, Petitioner turns to Kuo, arguing:

Kuo specifically discloses a method for “replacing or enhancing a tissue” that comprises “(a) forming a tissue construct by contacting a scaffold sheet of fibrous material with a cell; and rolling the scaffold sheet in a jelly-roll like manner to form a spirally wound tissue construct, (b) implanting the spirally wound tissue construct into a subject in need of tissue replacement or regeneration, wherein the spirally wound tissue construct replaces a tissue.” Kuo then states that the tissue to be replaced or regenerated is “*selected from the group consisting of a muscle, a nerve, a ligament, a tendon, or another tissue.*”

Id. (quoting Ex. 1018 ¶¶22–23, emphasis added)). Petitioner argues that it would have been obvious to use Huang2’s aligned fibers to fabricate a scaffold to treat a tendon, ligament, or a nerve defect in view of Kuo, which teaches the desirability of using aligned fibers for such applications. *Id.* at 39–40 (citing Ex. 1003 ¶¶131, 133–135; Ex. 1018 ¶¶6, 34, 112).

Patent Owner argues “Kuo’s treatment of [tendon, ligament, and nerve] tissues turns on its unique ‘jelly-roll’ structure. But Huang2 does not disclose a rolled scaffold” PO Resp. 32. This argument is unpersuasive because it attacks the references individually. *See In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (“Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references.”). Petitioner explicitly asserts that a person of ordinary skill would have “use[d] Huang2’s aligned fibers . . . to fabricate a scaffold to treat a tendon, ligament, or a nerve defect *as taught by Kuo.*” Pet. 39–40 (citing Ex. 1003 ¶131, emphasis added). And, in reply to Patent Owner’s arguments, Petitioner provides a step-by-step description of how a person of ordinary skill in the art would go about

it. *See* Pet. Reply 14–17 (discussing among other things Kuo Figure 1). Kuo Figure 1 is reproduced below.



Ex. 1018, Fig. 1. Figure 1, reproduced above, shows a schematic flowchart of Kuo’s “fabrication of a tissue construct.” *Id.* ¶28. In a nutshell, Petitioner proposes using Huang2 for the first illustrated step (“Prepared scaffolds”) and then continue following Kuo’s process. *See* Pet. Reply 16 (“[T]here was motivation to use the flat sheet aligned scaffold of Huang2 as the first step of the Kuo schematic.”). In other words, in Petitioner’s proposed modification, Huang2’s flat scaffold would be rolled at the step shown above and labeled “Roll scaffold.”

We are cognizant, as Patent Owner points out (*see* PO Sur-Reply 18), that the Board’s Decision on Institution stated the following:

Petitioner does not address Kuo’s teaching regarding this rolled structure at all, let alone present any rationale to modify Huang2’s scaffolds to mimic this rolled structure of natural tendon, nerve, or ligament issue, or otherwise explain why a POSITA would not¹⁸ seek to mimic that rolled structure when developing a scaffold to repair those specific types of tissues.

¹⁸ It seems that inclusion of the word “not” was a typographical error, and that the verb phrase “would seek” was intended.

Inst. Dec. 33–34. However, that statement is incorrect, as the Petition certainly addressed Kuo’s teaching regarding the rolled structure.

Specifically, as part of a summary of the asserted prior art, the Petition noted that “Kuo reports how their ‘[a]ligned nanofiber scaffolds were seeded with progenitor cells and subsequently *rolled* with the leading edge parallel to the axis of alignment.’” Pet. 22 (quoting Ex. 1018 ¶112; emphasis added)).

And, in addressing the particular limitation in question, the Petition asserts:

Kuo specifically discloses a method for “replacing or enhancing a tissue” that comprises “(a) forming a tissue construct by contacting a scaffold sheet of fibrous material with a cell; and *rolling the scaffold sheet in a jelly-roll like manner to form a spirally wound tissue construct*, (b) implanting the spirally wound tissue construct into a subject in need of tissue replacement or regeneration, wherein the spirally wound tissue construct replaces a tissue.”

Pet. 39 (quoting Ex. 1018 ¶22, emphasis added)). The Petition also presented a sufficient rationale to modify Huang2’s scaffold to mimic the rolled structure of natural tendon, nerve, or ligament issue because the Petition demonstrated that Kuo explicitly teaches rolling a scaffold for such tissue applications.

Next Patent Owner points out that Huang2’s scaffold has an elastic modulus of 8.98 MPa, and argues that is thus unusable “to repair a tendon, a ligament or a nerve defect,” as recited in claim 1. PO Resp. 36 (citing Ex. 1005, 1794). More specifically, Patent Owner argues that Huang2’s scaffold would be “too compliant” to work for tendon and ligament applications and would have “too much stiffness” to work for nerve applications. *Id.* (citing Ex. 2015 ¶¶129, 132).

Petitioner replies that “the ’227 patent presents no working examples of using a scaffold to treat tendon, ligament, or nerve and is ‘entirely silent’

about elastic modulus, stiffness, and degradation rate, ‘suggesting that a person of ordinary skill in the art was more than capable of’ optimizing them.” Pet. Reply 19 (quoting *Uber Techs., Inc. v. X One, Inc.*, 957 F.3d 1334, 1339 (Fed. Cir. 2020)). Patent Owner does not dispute this point. PO Sur-Reply 23–24. Instead, Patent Owner argues that the Petition did not propose modifying Huang2’s elastic modulus and cannot do so “for the first time on Reply.” *Id.*

We are not persuaded that the elastic modulus was an impediment to a person of ordinary skill in the art or that Petitioner was obligated to address the matter in its Petition. To the contrary, the record supports that the person of ordinary skill knew how to modify the elastic modulus of a scaffold of aligned fibers and tailor it to the tissue application.

Finally, Patent Owner argues that “Huang2’s scaffold is designed only for skin tissue repair and is seeded with normal human dermal fibroblasts (‘NHDF’) to achieve that function.” PO Resp. 36–37. Thus, according to Patent Owner, a person of ordinary skill in the art “would not expect that scaffold to successfully promote tendon, ligament, or nerve repair because it is devoid of the cell types and scaffold structure needed to repair those tissue types.” *Id.* at 38. This is another attack on the references individually. Kuo teaches a seeding step (labeled “Add cells” in Kuo Figure 1), which is part of the teachings relied upon by Petitioner. *See* Ex. 1018, Fig. 1; Pet. 39–40 (asserting that a person of ordinary skill would have “use[d] Huang2’s aligned fibers . . . to fabricate a scaffold to treat a tendon, ligament, or a nerve defect *as taught by Kuo*”). Moreover, “[a] person of ordinary skill is also a person of ordinary creativity, not an automaton.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). We find wholly unpersuasive Patent Owner’s argument that a person of ordinary skill in the art, seeking to

heal a certain type of tissue, would blindly seed the scaffold with the wrong type of cells.

We have reviewed both parties' arguments and evidence, and we determine, based on a preponderance of the evidence, that claim 1 would have been obvious over Huang2 and Kuo.

2. Dependent Claim 2

Dependent claim 2 recites: "The method of claim 1, wherein the scaffold is in the form of one or more elongated sheets." Ex. 1001, 23:38–39.

Regarding the additional limitation added by claim 2, Petitioner relies on both Huang2 and Kuo. First, Appellant argues that the "electrospun fibers fabricated in Huang2 would constitute a sheet." Pet. 41 (internal quotations omitted). Second, Appellant directs us to certain paragraphs of Kuo that refer to "scaffold sheets." *Id.* (citing Ex. 1018 ¶¶7, 20, 22).

We are not persuaded by Appellant's citations to either reference. As discussed above, Petitioner's Ground 1 is premised on a person of ordinary skill in the art altering the native flat sheet structure of Huang2 by rolling it into a jelly-roll structure as taught by Kuo. *See* Pet. 41 (Beginning its claim 2 arguments with the following: "Claim 1 is obvious for the reasons expressed above in § X.A., *supra*, which are incorporated herein."); *see also* Pet. Reply 17 ("[B]ased on the explicit teaching of Kuo, a POSA would have been motivated to take the electrospun flat scaffold made by the techniques of Huang2, seed it with the desired cells, *and roll it* to treat a tendon and ligament." (emphasis added)). Indeed, the paragraphs of Kuo that Petitioner cites for disclosing "scaffold sheets," explicitly describe rolling them into jelly-roll like structures. *See* Ex. 1018 ¶7 (stating that "the sheet is spirally

wound in a jelly-roll like manner”), ¶20 (describing a “method comprising: contacting a scaffold sheet of fibrous material with a cell; and rolling the scaffold sheet in a jelly-roll like manner to form a spirally wound tissue construct”), ¶22 (describing a method comprising “forming a tissue construct by contacting a scaffold sheet of fibrous material with a cell; and rolling the scaffold sheet in a jelly-roll like manner to form a spirally wound tissue construct” and implanting it in a patient).

Petitioner fails to argue that that “one or more elongated sheets” recited in claim 2 would encompass the rolled structure of its proposed modification. Nor does Petitioner articulate a claim construction argument that could support such an argument.

Petitioner has failed to prove, by a preponderance of the evidence, that claim 2 would have been obvious over Huang² and Kuo.

3. Dependent Claim 3

Dependent claim 3 recites: “The method of claim 1, wherein the scaffold is a composite of multiple layers of one or more sheets.” Ex. 1001, 23:40–41.

Petitioner’s challenge to claim 3 is plagued by the same problem as its challenge to claim 2. *See* Pet. 41 (Beginning its claim 3 arguments with the following: “Claim 1 is obvious for the reasons expressed above in § X.A., *supra*, which are incorporated herein.”). In the proposed modification, Huang²’s scaffold is rolled into a structure that is not encompassed by the plain and ordinary meaning of the term “sheet” and Petitioner has not advanced a claim construction argument that would support its challenge.

Petitioner has failed to prove, by a preponderance of the evidence, that claim 3 would have been obvious over Huang² and Kuo.

4. Dependent Claim 4

Dependent claim 4 recites: “The method of claim 1, wherein the tissue defect is a the [sic] nerve defect.” Ex. 1001, 23:42–43.

Regarding the additional limitation added by claim 4, Petitioner cites Kuo’s teaching that its invention is useful for treating, among other types of tissue, nerve tissue. Pet. 43 (citing Ex. 1018 ¶¶22, 34, 52); *see also* Ex. 1003 ¶¶133, 135. Patent Owner does not present any separate arguments for dependent claim 4. PO Resp. 42.

We are persuaded, based on a preponderance of the evidence, that claim 4 would have been obvious over Huang² and Kuo.

5. Dependent Claim 5

Dependent claim 5 recites: “The method of claim 1, wherein the tissue defect is a the [sic] ligament defect.” Ex. 1001, 24:1–2.

Regarding the additional limitation added by claim 5, Petitioner cites Kuo’s teaching that its invention is useful for treating, among other things, ligament injuries. Pet. 43 (citing Ex. 1018 ¶¶6, 34, 67, 112); *see also* Ex. 1003 ¶¶133, 134. Patent Owner does not present any separate arguments for dependent claim 5. PO Resp. 42.

We are persuaded, based on a preponderance of the evidence, that claim 5 would have been obvious over Huang² and Kuo.

6. Dependent Claim 6

Dependent claim 6 recites: “The method of claim 1, wherein the tissue defect is a the [sic] tendon defect.” Ex. 1001, 24:3–4.

Regarding the additional limitation added by claim 6, Petitioner cites Kuo’s teaching that its invention is useful for treating, among other things, ligament injuries. Pet. 43 (citing Ex. 1018 ¶¶6, 34, 67, 112); *see also* Ex.

1003 ¶¶133, 134. Patent Owner does not present any separate arguments for dependent claim 6. PO Resp. 42.

We are persuaded, based on a preponderance of the evidence, that claim 6 would have been obvious over Huang² and Kuo.

E. Ground 2: Obviousness over Lee and Kuo

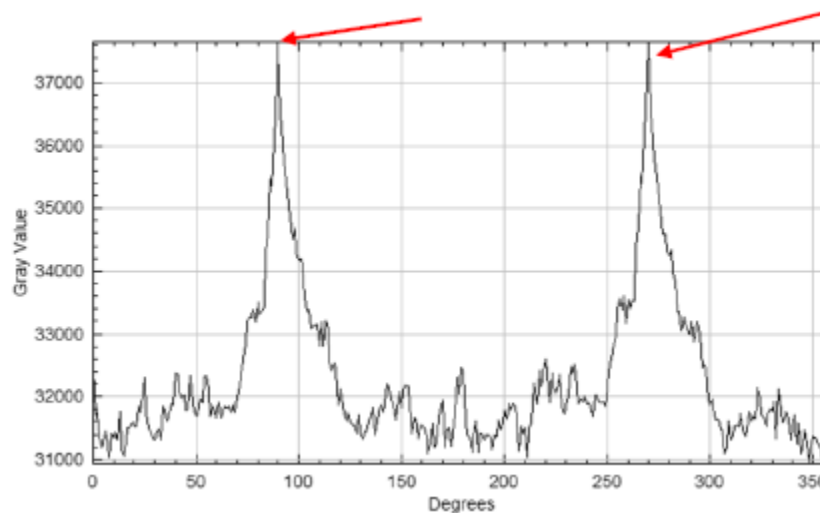
In Ground 1, Petitioner contends that claims 1–6 would have been obvious over Lee and Kuo. Pet. 45–59. As explained below, we find that Petitioner has failed to prove this contention.

Independent claim 1 recites, among other things, “wherein a result of a fast Fourier transform (FFT) analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other.” Ex. 1001, 23:32–35. For this limitation, Petitioner relies exclusively on Lee. Pet. 47–51.

Lee does not disclose an FFT analysis of its fibers. Petitioner, however, points to other teachings in Lee with regard to studying the impact of alignment and orientation of the electrospun PCL/collagen nanofibers on the performance and properties of the scaffolds. Pet. 47–51. In particular, Lee discloses that “[f]iber orientations were induced by electrospinning onto a collector at different rotation rates.” Ex. 1011 ¶61; *see* Pet. 48 (citing the same). Lee analyzed SEM images of the scaffolds with the “UTHSCSA ImageTool 3.0” to determine the average fiber diameters and fiber orientations within the nanofiber meshes. Ex. 1011 ¶66; *see* Pet. 48 (citing the same). Because the SEM images in Lee have poor image quality, Petitioner points to images from Lee’s provisional application serial no. 61/025,350 (“Lee’s provisional application”; Ex. 1021) as showing the same data, but with clearer images. Pet. 48–49; *see* Ex. 1021, 38 (Figs. 1D, 1H).

Petitioner contends that the image analysis from the figures in Lee's provisional application show that Lee discloses "highly aligned fibers." Pet. 49.

Although Lee does not disclose an FFT analysis, Petitioner contends that a POSITA "would know that the degree of alignment could also be determined using ImageJ software to run an 'FFT analysis' on the images published in Lee." *Id.* at 50 (citing Ex. 1003 ¶181). Petitioner contends that such an application of the ImageJ software was well known at the time of Lee's filing, and the use of such an FFT analysis would confirm fiber alignment. *Id.* at 50. Petitioner further points to Dr. Simpson's own FFT analysis based on Figure 1D of Lee's provisional, which produced the following plot:



Pet. 50. Dr. Simpson explains that he conducted his own analysis of Lee's Figure 1D using the FFT methodology identified in the '227 patent (based on the Ayres 2008 paper), and reported the data from 0° to 360° as shown above. Ex. 1003 ¶183. As explained by Dr. Simpson, the graph above demonstrates that the aligned fibers have a first major peak at about 90° and

a second major peak at about 270° (annotated with red arrows), which shows the peaks are about 180° apart as recited in claim 1. *Id.* ¶184.

Patent Owner argues that (1) Petitioner’s arguments about what a theoretical FFT analysis result might show in regards to Lee’s scaffold are “unclear” and (2) Dr. Simpson’s FFT analysis was faulty and is “entitled to no weight.” PO Resp. 43, 49.

Relevant to Patent Owner’s first point, the Institution Decision stated the following:

Petitioner does not clearly assert in the Petition that the fibers taught by Lee necessarily or inherently satisfy the claimed FFT analysis result. Petitioner’s grounds based on Lee may ultimately fail on the merits due to this lack of specificity.

Inst. Dec. 36. We agree with that initial analysis—that the Petition does not assert that the fibers taught by Lee necessarily or inherently satisfy the FFT analysis requirement.

In its Reply, Petitioner attempts to persuade us otherwise, asserting that “the Petition specifically asserts inherency.” Pet. Reply 24. According to Petitioner:

The Petition asserts that performing an FFT analysis on Lee’s fibers “would show” that the fibers are aligned, and the Petition then presents an FFT analysis that confirms “adjacent major peaks at around 90° and 270°.” (Paper-2, 50.) The phrase “would show” indicates that the claimed peaks are a necessary result of performing an FFT analysis on Lee’s fibers. *See Arbutus Biopharma Corporation v. ModernaTX, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023) (explaining that the standard for inherent anticipation is whether the practice of the prior art “would result in the claimed product.”) This portion of the Petition further cites Dr. Simpson, who stated in his declaration that the FFT peaks obtained by his testing “are a *natural and necessarily present* property of the fibers that Lee discloses,” which is the hallmark for inherency. (EX1003, ¶185 (incorporated into Paper-2, 50).)

Pet. Reply 24. Petitioner is combining arguments that were presented separately in the Petition about, on the one hand, what a theoretical FFT analysis result that could be performed would show and, on the other hand, what Dr. Simpson's FFT analysis result purportedly shows.

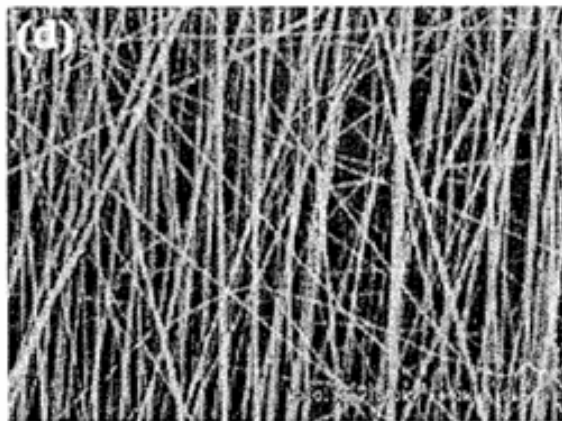
First, the Petition uses the phrase "would show" in reference to an FFT analysis result showing aligned fibers, not in reference to an FFT analysis result having adjacent major peaks with about 180° apart from each other. *See* Pet. 50 ("[I]f a POSA wanted to perform an FFT analysis on the SEM image in Lee, . . . [t]his *would show the fibers were oriented on the scaffold in Lee in an aligned manner.*" (emphasis added)). Second, Petitioner's argument that "the Petition then presents an FFT analysis that confirms 'adjacent major peaks at around 90° and 270°'" (Pet. Reply 24) is referring to what Dr. Simpson's FFT analysis result purportedly shows. *See* Pet. 50–51 ("Petitioners' expert, Dr. Simpson, ran an FFT analysis on Lee's Figure 1D" and "[t]he resulting graph shows clear adjacent major peaks at around 90° and 270°.").

Nowhere *in the Petition* does Petitioner argue that an FFT analysis result of Lee's fibers necessarily or inherently would have major peaks with about 180° apart from each other. This is not to say that the evidence of record could not support such an assertion. In fact, it clearly does, as Lee disclosed a scaffold of aligned fibers. But *the Petition* did not assert inherent disclosure of the FFT limitation with particularity. *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) ("In an IPR, the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable."); 35 U.S.C. § 312(a)(3) (requiring that "the petition identifies in writing and *with particularity*, each claim

challenged, the grounds on which the challenge to each claim is based”) (emphasis added).

We turn now to Petitioner’s theory based on the results of Dr. Simpson’s actually performed FFT analysis. Petitioner argues that its “expert, Dr. Simpson, ran an FFT analysis on Figure 1D.” Pet. 50. The resulting graph is included on page 50 of the Petition and is reproduced *supra*. It shows major peaks with about 180° apart from each other. Pet. 50; *see also* Ex. 1003 ¶¶183–184 (Dr. Simpson reproducing and interpreting the graph).

Patent Owner argues that “Dr. Simpson’s testing is inconsistent with the ’227 patent.” PO Resp. 49. In particular, Patent Owner argues that Dr. Simpson “did *not* test high quality images” and instead used “a remarkably poor-quality photocopy of a SEM image, as shown below (which did not even come from Lee, but instead from Lee’s provisional application).” *Id.* The SEM image from Lee’s provisional application is reproduced below.



Ex. 1021, 38 (Fig. 1D). Figure 1D, reproduced above, is the image Dr. Simpson used for his FFT analysis. Ex. 1003 ¶179. Patent Owner argues that, “[i]mmediately apparent from visual inspection of this image is its poor quality with a facial lack of contrast between individual fibers, especially among fibers toward the background of Lee’s scaffold.” PO Resp. 50.

Patent Owner's witness, Dr. Mikos, testifies that "[a] POSITA would never conduct FFT analysis on such an image . . . because this image includes a remarkable amount of noise and lacks necessary contrast between individual fibers, especially regarding deeper fibers that appear toward the visual background of Lee's image." *Id.* (alteration in original) (quoting Ex. 2015 ¶164).

During cross-examination, Dr. Simpson confirmed that he used a photocopy of Figure 1D from Lee's provisional application.

Q. What was your first step in performing FFT analysis on the Lee provisional Figure 1-D?

A. I selected my square from the middle of the rectangle, trimmed the image, and then conducted the FFT

Q. So you didn't do your FFT analysis on the actual image that Lee captured with SEM, did you?

A. That was not available to me.

Q. So what you analyzed was a Xerox or a photocopy?

A. This image, yes.

Q. Okay. So it was a photocopy?

A. It was this photocopy.

Ex. 2017, 156:16–157:4. Dr. Simpson further testified that he does not normally do FFT analyses using photocopied images and does not advise his students to do so either. *Id.* at 157:8–158:3.

The fact that Dr. Simpson employed Figure 1D from Lee's provisional application as opposed to Figure 1D from Lee itself suggests that he agrees that poor image quality is detrimental to an accurate FFT analysis. Figure 1D of Lee's provisional application, although of better quality than that of Lee itself, nonetheless appears to be of fairly poor quality. Indeed, Dr. Simpson used it "out of necessity." *Id.* at 157:10–12.

In its Reply, Petitioner argues that “Dr. Simpson has shown that large amounts of noise do [sic, not] prevent an FFT of aligned fibers from demonstrating the claimed FFT peaks.” Pet. Reply 25 (citing Ex. 1219, ¶75). Patent Owner argues that the cited declaration testimony, which was submitted with the Reply, “is belied by earlier statements.” PO Sur-Reply 27. For example, Patent Owner points out that Ayres 2008, co-written by Dr. Simpson, states that images “composed largely of optical noise . . . are unsuitable for [FFT] analysis.” *Id.* (quoting Ex. 1010, 605). Patent Owner also points out that Ayres 2006, also co-written by Dr. Simpson, states that “noise can degrade the absolute alignment value assigned to a scaffold by FFT analysis.” *Id.* (quoting Ex. 1013, 7).

It is clear from the record before us that image quality is important and that too much noise can render an FFT analysis unreliable. It is not, however, clear how much noise is too much noise. That said, it is Petitioner’s burden to prove unpatentability; it is not Patent Owner’s burden to prove the opposite. Based on the evidence of record, we find that Petitioner has not met its burden given the irregular nature of Dr. Simpson’s FFT analysis (using a photocopy of a SEM image that bears significant noise).

For the foregoing reasons, Petitioner has not proven that Lee discloses “wherein a result of a fast Fourier transform (FFT) analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other.” Thus, Petitioner’s contention that claims 1–6 would have been obvious over Lee and Kuo, which is premised on Lee disclosing this limitation, fails.

F. Ground 3: Anticipation by Huang2

In Ground 3, Petitioner contends that claims 7 and 8 are anticipated by Huang2. Pet. 47–64. As explained below, we find that Petitioner has proven by a preponderance of evidence that Huang2 anticipates claims 7 and 8.

1. Independent Claim 7

Independent claim 7 recites “[a] method of cell culture comprising placing cells on a scaffold comprising aligned fibers.” Ex. 1001, 24:5–6. Regarding this limitation, Petitioner argues that Huang2 discloses “plac[ing] cells, fibroblasts, on a scaffold containing both aligned and unaligned fibers to determine how the alignment affects cell growth and behavior on the scaffold.” Pet. 59 (citing Ex. 1005, 1791). As noted by Petitioner, Huang2 states: “Normal human dermal fibroblasts (NHDFs) were seeded on collagen-containing PCL nanofibrous matrices with either isotropic nanofiber arrangement (i.e., randomly collected nanofibers with no alignment, abbreviated as “Iso”) or anisotropic nanofiber arrangement (i.e., collected nanofibers with alignment, abbreviated as “Aniso”).” *Id.* (quoting Ex. 1005, 1792). Patent Owner does not dispute that Huang2 discloses a method of cell culture comprising placing cells on a scaffold comprising aligned fibers, as argued by Petitioner. PO Resp. 65. We are persuaded that Huang2 does.

Claim 7 also recites “wherein a result of a FFT analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other.” Ex. 1001, 24:7–9. As discussed above in Ground 1, Petitioner has shown that Huang2 discloses this limitation. *See* PO Resp. 65 (Patent Owner standing on its Ground 1 arguments for this limitation).

Lastly, claim 7 recites “growing the cells in conditions suitable for the cell culture.” Ex. 1001, 24:10–11. With regard to this limitation, Petitioner argues that “Huang2 teaches culturing fibroblasts under suitable conditions such that the cells grow.” Pet. 61. More specifically, Petitioner cites Huang2’s disclosure that “fibroblasts were seeded on the nanofibrous matrices at a density of 5×10^3 cells/cm² and allowed to attach for 60 min before fully supplemented media was added. The cells were cultured on the isotropic or anisotropic nanofibrous matrices for up to 7 days.” *Id.* (quoting Ex. 1005, 1792). Petitioner also cites Huang2’s disclosure that “[i]n order to evaluate the effects of various fiber organizations (*i.e.*, isotropic vs. anisotropic) on [normal human dermal fibroblast] migration, an *in vitro* wound healing assay was performed by culturing cells on various matrices with ‘wound gaps’ created by an insert (Fig. 6A).” *Id.* (alteration in original) (quoting Ex. 1005, 1796); *see also* Ex. 1005, Fig. 6. Patent Owner does not dispute that Huang2 discloses growing the cells in conditions suitable for the cell culture, as argued by Petitioner. PO Resp. 65. We are persuaded that Huang2 does.

We are persuaded, based on a preponderance of the evidence, that claim 7 is anticipated by Huang2.

2. Dependent Claim 8

Claim 8 recites: “The method of claim 7, wherein the cells are stem cells, adipose derived stem cells, dental pulp stem cells, *fibroblasts*, and/or dorsal root ganglia.” Ex. 1001, 24:12–14 (emphasis added).

With regard to the additional limitation added by claim 8, Petitioner again relies on Huang2’s disclosure that “fibroblasts were seeded on the nanofibrous matrices at a density of 5×10^3 cells/cm² and allowed to attach

for 60 min before fully supplemented media was added. The cells were cultured on the isotropic or anisotropic nanofibrous matrices for up to 7 days.” Pet. 62–63 (quoting Ex. 1005, 1792). Patent Owner does not present any separate arguments for dependent claim 8. PO Resp. 42.

We are persuaded, based on a preponderance of the evidence, that claim 8 is anticipated by Huang2.

III.CONCLUSION

Based on a preponderance of the evidence, Petitioner has shown that claims 1 and 4–8 are unpatentable but has failed to show that claims 2 and 3 are unpatentable. In summary:

Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1–6	103	Huang2, Kuo	1, 4–6	2, 3
1–6	103	Lee, Kuo		1–6
7, 8	102	Huang2	7, 8	
Overall Outcome			1, 4–8	2, 3

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1 and 4–8 of U.S. Patent No. 11,318,227 B2 are unpatentable as challenged;

FURTHER ORDERED that claims 2 and 3 of U.S. Patent No. 11,318,227 B2 are not unpatentable as challenged; and

FURTHER ORDERED that that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial on the grounds of unpatentability authorized above; the trial commences on the entry date of this decision.

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