

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

EMBODY, INC. AND ZIMMER BIOMET HOLDINGS, INC.,
Petitioners

v.

LIFENET HEALTH,
Patent-Owner.

Case IPR2025-00249
U.S. Patent No. 11,318,227

REPLY TO PATENT-OWNER'S RESPONSE

Filed on behalf of Petitioner

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PETITIONERS' LIST OF EXHIBITS

Exhibit No.	Description	Previously Submitted
1001	U.S. Patent No. 11,318,227 to Francis et al. (“the ’227 patent”)	x
1002	’227 Patent Prosecution History	x
1003	Declaration of David G. Simpson, Ph.D.	x
1004	CV of David G. Simpson, Ph.D.	x
1005	Huang et al., <i>The involvement of integrin $\beta 1$ signaling in the migration and myofibroblastic differentiation of skin fibroblasts on anisotropic collagen-containing nanofibers</i> , 33 Biomaterials 1791-1800 (Feb. 2012) (“Huang2”) (available online Dec. 2, 2011)	x
1006	Kumbar et al., <i>Electrospun nanofiber scaffolds: engineering soft tissues</i> , Biomed. Mater. 3 (2008) (“Kumbar”)	x
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1009	U.S. Patent App. Pub. No. 2004/0037813 to Simpson et al. (“Simpson”)	x
1010	Ayres et al., <i>Measuring fiber alignment in electrospun scaffolds: a user’s guide to the 2D fast Fourier transform approach</i> , 19 J. Biomater. Sci. Polymer. 603-621 (2008) (“Ayres 2008”)	x
1011	Lee et al., U.S. Patent Application No. US 2010/0331980 A1, Pub. Date December 1, 2011 (“Lee”)	x
1012	Reserved	
1013	Ayres et al., <i>Modulation of Anisotropy in Electrospun Tissue Engineering Scaffolds: Analysis of Fiber Alignment by the Fast Fourier Transform</i> , 27(32) Biomaterials 5524-5534 (2006) (“Ayres 2006”)	X
1014	U.S. Pat. No. 5,514,378 to Mikos (“Mikos”)	x
1015	Jose et al, <i>Fabrication and Characterization of Aligned Nanofibrous PLGA/Collagen Blends as Bone Tissue Scaffolds</i> , 50 Polymer 3778-85 (2009) (“Jose”)	x

1016	Fu et al, <i>Spatial Arrangement of Polycaprolactone/Collagen Nanofiber Scaffolds Regulates the Wound Healing Related Behaviors of Human Adipose Stromal Cells</i> , 18(5) Tissue Engineering, 631-42 (2012) (“Fu”)	x
1017	Shoulders & Raines, <i>Collagen Structure and Stability</i> , 78 Annu. Rev. Biochem. 929 (2009)	x
1018	Kuo et al., U.S. Patent Application No. US 2011/0293685 A1, Pub. Date Dec. 1, 2011 (“Kuo”)	x
1019	Beachley et al, <i>Highly Aligned Polymer Nanofiber Structures: Fabrication and Applications in Tissue Engineering</i> (2011) in Vol. 246 Biomedical Applications of Polymeric Nanofibers (Jayakumar & Nair eds. 2011)	x
1020	Declaration of Emma Xu	x
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1024	June 21, 2022 Memo From Katherine Vidal on Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation (June 21, 2022), available at https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_.pdf	x
1100	<i>LifeNet Health v. Zimmer Biomet Holdings, Inc.</i> , 23- cv- 00479, D.I. 41 (10/09/24)	x
1101	ZIMMER BIOMET, <i>Patent Marking List for Website Q1-2025</i> , Last updated Mar. 19, 2025, available at https://www.zimmerbiomet.com/content/dam/zbcorporate/en/corporate/patents/Patent-Marking-Listfor-Website-Q1-2025.pdf (last visited Sept. 9, 2025)	x

1203	Smoak et al, <i>Bioinspired Electrospun dECM Scaffolds Guide Cell Growth and Control the Formation of Myotubes</i> , 7(20) Sci Adv at 1 (May 2021)	
1204	Dilorio et al, <i>Understanding Tendon Fibroblast Biology and Heterogeneity</i> , 12(4) Biomedicines 859 (2024)	
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I. INTRODUCTION

The record confirms that the asserted claims of U.S. Patent No. 11,318,227 (“the ’227 patent”) are obvious in view of the prior art, primarily Huang², Kuo, and Lee. That prior art, not previously considered during prosecution, establishes that aligned collagen fibers were well-known in the art, and that it would have been obvious to use such fibers to treat a tendon, ligament, or nerve.

Recognizing this problem, Patent-Owner shifts course in its Patent-Owner Response (“POR”) and raises a new claim construction never before raised. Patent-Owner asserts that the claims are not directed to aligned collagen fibers but require a minimum of four FFT peaks to calculate an arithmetic mean to establish fiber alignment. Yet neither the ’227 patent, Ayres²⁰⁰⁸, the prosecution history, nor any cited prior art discloses such a calculation or requirement. Patent-Owner’s position thus depends on an analytical framework that appears nowhere in the intrinsic or extrinsic record. Indeed, Patent-Owner’s new construction would improperly sweep within the claims the very embodiment that the specification itself identifies as depicting random fibers outside the claims.

Further, in arguing that there was no motivation to combine either Huang² or Lee with Kuo, the Patent-Owner mischaracterizes both the arguments set forth in the Petition and the prior art relied therein. The Patent-Owner also seeks to impose requirements in the prior art that are missing in the patent as to how to

practice the invention. This is improper according to well-established law.

Accordingly, Petitioners respectfully request that Board find the claims unpatentable.

II. ARGUMENT

A. Patent-Owner's Claim Construction Argument is Flawed

Patent-Owner's main argument in its Patent-Owner Preliminary Response ("POPR") was that one FFT peak in a 180° degree field is not sufficient to show two peaks in a 360° field, as required by the claims. (Paper-8, 15–16.) This argument, however, was refuted by Ayres2008, which is incorporated by reference into the '227 patent. Ayres2008, as noted by the Board, explains that the results of an FFT plot are symmetrical through 360° and that only data through 180° need be depicted based on this symmetry. In other words, a single peak in the 180° field *necessarily* shows a symmetrical peak at 180° apart if all 360° were depicted. (Paper-13, 25–26; Paper-2, 12, 37; EX1010, 609.)

Recognizing this weakness, the Patent-Owner now advances a claim construction argument, missing from its POPR, that it argues excludes Huang2 as invalidating prior art. (Paper-23, 6–9, 17.) Patent-Owner asserts that the term "major peaks" is expressly defined in the '227 patent and that the patentee acted as its own lexicographer. Patent-Owner relies on the statement that "[t]he 'major

peaks’ herein refer to peaks higher than the average of the peaks in the result.”

(EX1001, 13:28–29.) But this lexicography argument fails.

To invoke lexicography, the alleged definition must be clear, deliberate, and unambiguous such that a person of ordinary skill in the art would readily understand the scope of the term. *See Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1477 (Fed. Cir. 1998). Initially, the claim term is not “major peaks,” but instead, “major adjacent peaks,” which is not defined. Moreover, even if the applicants meant to define the phrase, “major peaks,” there is still a question of what the phrase “peaks higher than the average of the peaks in the result” means to a POSA in the context of an alignment plot obtained by following the Ayres2008 method. And what Patent-Owner says this phrase means is *not* correct. *See Kumar v. Ovonic Battery Co., Inc.*, 351 F.3d 1364, 1368 (Fed. Cir. 2003). There, the Federal Circuit found the claim term “amorphous” was controlled by a definition and meant “exhibit[ing] no long range order.” *Id.* Nevertheless, the Federal Circuit found that the words “no long range order” were unclear in the context of the invention and remanded for further claim construction. *Id.* at 1372.

Patent-Owner asserts that determining the “average of the peaks in the result” requires a specific multi-step numerical procedure that is not described in the ’227 patent, Ayres2008, or any other prior art. According to Patent-Owner, one must first identify all peaks in an FFT plot, assign numerical values to the height of

each peak, calculate an arithmetic mean of those height values, and then designate as “major peaks” only those peaks exceeding that mean. (Paper-23, 8-9; EX1219, ¶4.)

Patent-Owner then argues that because Huang2 discloses only one peak in a 180-degree field, or two peaks of equal height in a 360-degree field, the average would equal the peak values themselves, such that neither peak would be higher than the average and thus neither would qualify as “major.” (*Id.*, 17.) On that basis, Patent-Owner contends that Huang2 does not disclose “major peaks” within the meaning of claim 1 and therefore cannot invalidate the ’227 patent.

This argument is fundamentally flawed. Patent-Owner’s proposed numerical averaging approach is nowhere disclosed in the specification. Moreover, the approach directly contradicts Ayres2008, which the ’227 patent incorporates by reference as the authoritative guide for performing FFT analysis, as well as the specification’s express teachings and the prosecution history. (EX1219, ¶¶4, 7-10)

1. Patent-Owner’s Claim Construction is Inconsistent with the Specification and Ayres2008

Neither the ’227 patent nor Ayres2008 describes summing peak values, calculating an arithmetic mean, and using that mean to determine fiber alignment. (EX1220, 63:6-9, 86:3-5, 95:1-7; EX1219, ¶¶7-10.) If such a calculation were central to the claimed invention, the patent would necessarily describe how to perform it. It does not. The ’227 patent does not even label or numerically identify

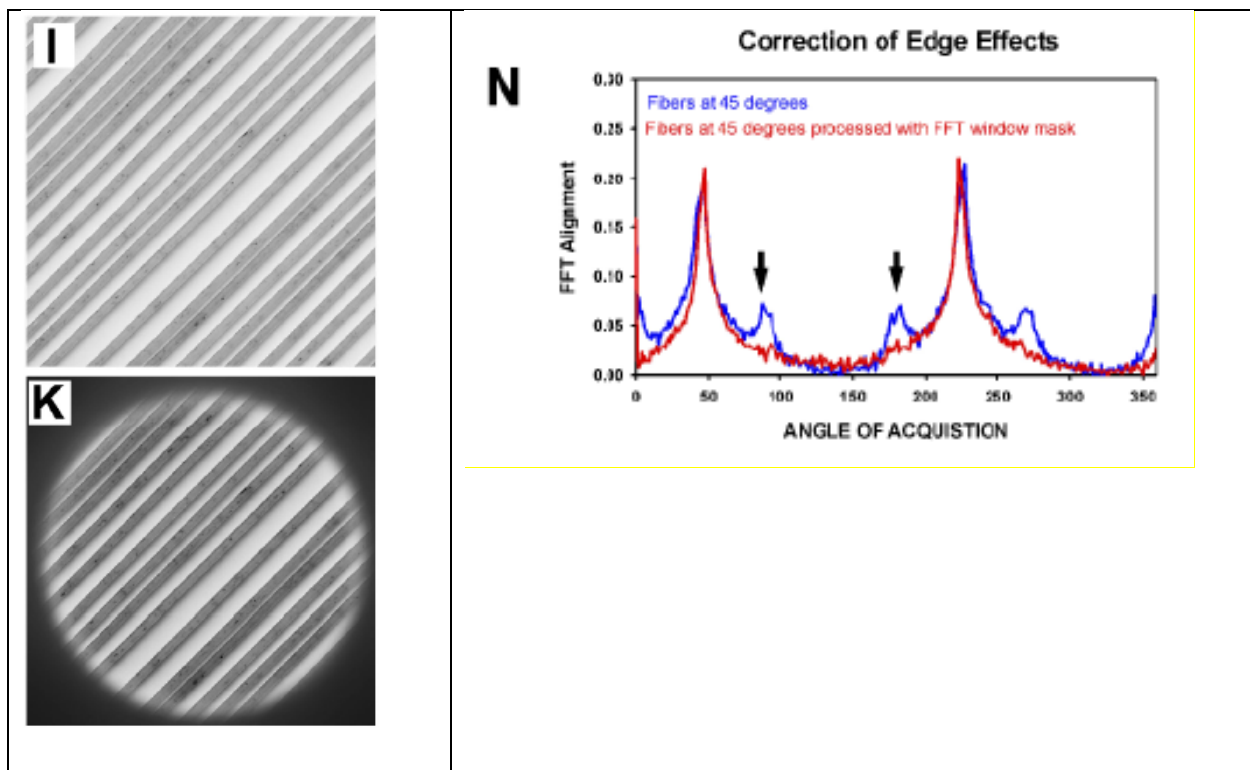
peaks in Figures 8A or 8B, the only FFT alignment plots disclosed. (EX1001; *see also* EX1220, 64:6–17; EX1219, ¶10.)

Instead, the '227 patent directs a POSA to Ayres2008, which it incorporates. Ayres carries out a *visual assessment* of the relative sizes and shape of the peaks to determine which peaks are “major” and thus indicate scaffold alignment.

Ayres2008 explains that: “The 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). The 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.” (EX1010, 610 (emphasis added); *see also* EX1220, 76:7-12.) “The overall 2D FFT alignment value for a scaffold *is determined by visually inspecting and selecting* the maximal value from the peak of the alignment plot.” (EX1010, 613 (emphasis added).) This is how a POSA would understand the phrase “major peaks” in the context of the '227 patent and is the correct claim construction. (EX1219, ¶¶5-6.) This is *not* a calculation based on the average of the height of the peaks in a plot.

This understanding was confirmed by Dr. Simpson, the senior author of Ayres2008, who testified that identifying “major peaks” is a visual comparison of relative peak height and shape and that references to an “average” reflect this qualitative assessment, not a numerical calculation. (EX2017, 88:6–89:9.)

Ayres2008 also provides concrete examples. In Figure 3, Ayres2008 presents FFT plots of a highly aligned scaffold. The blue trace contains additional peaks caused by edge-effect noise (designated by arrows), while the red trace uses masking to eliminate artifacts and shows only two peaks, accurately reflecting complete alignment. (EX1010, 614–15; EX1219, ¶¶13-14.)



Both plots represent the *same* aligned fibers, but the red trace is more accurate precisely because it removes noise. Yet under Patent-Owner’s proposed construction, the accurate red trace would fall outside the claims, while the noisy blue trace would fall within them. (EX1220, 83:21–84:23; EX1219, ¶15.) That

result is nonsensical and contradicts the teachings of Ayres2008. (EX1219, ¶16); see *AstraZeneca AB v. Mylan Pharms. Inc.*, 19 F.4th 1325, 1329 (Fed. Cir. 2021) (selecting the claim construction that “most naturally aligns with the patent’s description of the invention”). The same is true of Huang2. Because the fibers in Huang2 are highly aligned, its FFT plot reflects only two major peaks 180° apart when extended to 360°. (EX1219, ¶17.)

Patent-Owner’s claim construction effectively limits the claims to FFT plots that contain noise or imperfections. Indeed, Patent-Owner’s expert, Dr. Mikos, testified that his claim construction would require the presence of some misaligned fibers to generate additional peaks. (EX1220, 79:2–13, 80:6–16.) Nothing in the patent suggests that misalignment is required to practice the claimed invention. (EX1219, ¶¶11-12.)

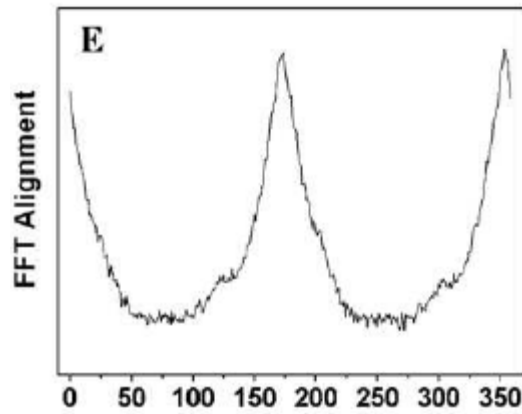
Patent-Owner’s claim construction collapses when applied to the patent’s own examples. According to the specification, Figure 8A shows aligned fibers and Figure 8B shows random fibers, which the patent terms a “control.” (Paper-23, 5; EX2015, ¶ 51; EX1001, 2:10-12; EX1219, ¶18.) Yet under Patent-Owner’s claim construction, the FFT plot for Figure 8B would fall within claim 1 because two of its four peaks exceed the calculated average and thus would be considered adjacent major peaks 180° apart. (EX1219, ¶19.) Patent-Owner’s expert, Dr. Mikos, also testified as to the height of the four peaks in figure 8B. (EX1220, 65:6-66:11, 69:2-

23.) Taking the average—as Dr. Mikos asserts one must do—would mean that two peaks 180° apart exceed the average and thus fall within the scope of the claims. Patent-Owner’s claim construction thus captures the patent’s control example of random fibers and interprets them as aligned, which cannot be correct. (EX1219, ¶19.) In contrast, Ayres2008’s visual test explains that four peaks of “nearly uniform height” indicate random fibers. (EX1010, 609.) Thus, under the Ayres2008 visual test, which is part of the patent specification, the random control sample would *not* fall within the scope of the claims, which is what the specifications teaches, and is thus how a POSA would understand the claims. (EX1219, ¶¶19-20.)

2. Patent-Owner’s Claim Construction is Contradicted by the Prosecution History

Patent-Owner’s claim construction is also contradicted by the prosecution history, which should be assessed. *AstraZeneca AB*, 19 F.4th at 1335. During prosecution, the Examiner rejected the claims of the parent ’223 patent in view of Huang1 (Fig. 4E), which discloses only two peaks at “175 degrees and 355 degrees (180 degrees apart)” in a scaffold with fibers made from pure TPU. (EX1007, 211; EX1008, 309, Fig. 4E; EX1220, 92:2-17.)¹

¹ In an FFT, the peaks at 0° and 355° are the same. (EX1220, 62:16-20.)



Patent-Owner did not dispute that those peaks were “major.” Instead, Patent-Owner amended the claims to require collagen, asserting that Huang1’s collagen containing scaffold did not show aligned fibers. (EX1007, 238.) However, under Patent-Owner’s construction, Fig. 4E of Huang1 would disclose no major peaks, contradicting the Examiner’s rejection and Patent-Owner’s amendment.

3. Patent-Owner’s Claim Construction Contradicts Its Position at the District Court

Patent-Owner’s current numeric averaging also contradicts its infringement position in district court, where no peak averaging was performed by Patent-Owner prior to filing suit. Instead, Patent-Owner relied on statements that Embody’s ActivBraid product, accused of infringing the ’227 patent, was “highly aligned.” (EX2005, ¶59.) Patent-Owner cannot adopt one claim construction to avoid invalidity while asserting another for infringement. *Paypal Holdings, Inc. v. Fintiv, Inc.*, IPR2023-00744, 2024 WL 4375951, at *8 (PTAB Oct. 2, 2024).

4. Patent-Owner's Claim Construction Relies on an Expert with No Applicable Experience with FFT

Patent-Owner's new claim construction rests entirely on the testimony of its expert, Dr. Mikos. But Dr. Mikos could not identify a publication where he used FFT analysis to generate an alignment plot of the sort described in Ayres2008 and depicted in the '227 patent. (EX1220, 32:8–20, 35:2–36:17, 52:8–20; EX1219, ¶24.) Thus, Patent-Owner's proposed construction is not grounded in the patent, the prior art, or Dr. Mikos's experience. Further, Dr. Mikos attempts to redefine the POSA by requiring an engineering degree should be rejected. (EX2015, ¶39.) That assertion is unsupported and contrary to the field, as shown by Dr. Simpson's own qualifications. (EX1219, ¶25.)

B. Huang2 Discloses Two Major Peaks in the FFT as Recited by Claim 1

A POSA would understand that Huang2 shows two major peaks in the FFT 180° apart by a visual analysis (Paper-2, 35–39; Paper-13, 26–27; EX1219, ¶¶21–23), which satisfies the claimed FFT element. And Dr. Simpson's testing confirmed there are two peaks if the plot were extended to 360°. (Paper-2, 37–39; Paper-13, 27–28.) Further, both the Petition (and Dr. Simpson's declaration) stated, as noted by the Board on institution, that the two peaks are “necessarily” there. (Paper-2, 28, 37; EX1003, ¶¶90, 121, 124.)

In response, Patent-Owner conducted no testing of its own and instead criticizes Dr. Simpson's analysis by challenging certain details, arguing that the inventor of the method does not know how to perform the method he himself developed. (See EX1219, ¶¶26-27.) Patent-Owner never explains how any of the alleged deficiencies in Dr. Simpson's analysis would alter the results, which alone defeats its arguments. Dr. Simpson, who invented and published the Ayres2008 method, should be credited over Dr. Mikos, who has never performed the Ayres2008 method or published a paper including an FFT plot.

Patent-Owner contends that Dr. Simpson's testing is invalid because he did not specify details such as illumination, noise, image type, software version, circular projection placement, or masking. (Paper-23, 21–22, 29–30.) But Dr. Simpson explained that he performed the analysis in accordance with Ayres2008, which is precisely the level of detail provided in the '227 patent. (EX1001, 13:38–46.) As Dr. Mikos admitted, none of the details Patent-Owner now demands appear in the '227 patent. (EX1220, 116:2–12, 117:10–16, 118:1–10; EX1219, ¶¶28.) A POSA would thus know how to carry out the Ayres2008 method, particularly its inventor. Patent-Owner cannot require more detail in the prior art than appears in the challenged patent. *See Uber Techs., Inc. v. X One, Inc.*, 957 F.3d 1334, 1339 (Fed. Cir. 2020); *In re Publicover*, 813 F. App'x 527, 532 (Fed. Cir. 2020);

Donghee Am., Inc. v. Plastic Omnium Advanced Innovation & Research, IPR2017-01633, 2019 WL 80465, at *5 (PTAB Jan. 2, 2019).

Dr. Simpson addresses and rebuts Dr. Mikos's criticisms in his supplemental declaration. (EX1219, ¶¶ 29-39.) With respect to masking, Ayres2008 teaches the use of masking to reduce noise, and Dr. Simpson explained that a POSA would understand when masking is appropriate. (EX2017, Tr. 208:18-209:18.) Dr. Simpson also performed FFT analyses both with and without masking, and both demonstrate the requisite peaks. (EX1219, ¶39.) As to image quality, Dr. Simpson testified that the image from Huang2 was more than sufficient, that FFT is a "pretty forgiving" technique," that even an "imperfect image can be used," and that Biomaterials would not have published Huang2 without an adequate image. (EX1220, 61:11-15, 138:23-139:14, 142:10-18.) Dr. Simpson also shows that even if one degrades the image from Huang2, one still obtains the required two major peaks. (EX1219, ¶ 35.) Patent-Owner's suggestion that FFT analysis may be performed only on "original" data would preclude FFT analysis of any published image, no matter how clear, and should be rejected. Ayres2006 did not even perform FFT on original data. (EX1219, ¶30.)

Patent-Owner argues that Dr. Simpson's testing is unreliable because it has additional small peaks and thus is different from the FFT in Huang2. (Paper-23, 25-28.) But, Ayres2008 states that the smaller peaks, like the ones in Dr.

Simpson's FFT plot, generally correspond to "background noise." (EX1010, 615; EX2017, 92:12-15, 118:13-119:5; EX1219, ¶ 40.) Moreover, both Dr. Simpson's FFT and the FFT in Huang2 disclose only one major peak in a 180° field and are thus perfectly consistent. (EX1219, ¶ 40.) Any differences likely result from the fact that the FFT plot in Huang2 may represent the average plot of separate FFT analysis run on five different images taken of different parts of the scaffold. (See Paper-23, 22–24; EX2015, ¶90; EX1220, 100:16-101:14; EX1219, ¶41.) In contrast, Dr. Simpson ran his FFT on the single image that was published in Huang2. (*Id.*) This difference explains why Huang2's FFT plot is not identical to that run by Dr. Simpson. (*Id.*)

C. Dr. Simpson's Testing Meets Even Patent-Owner's Construction

Petitioners can respond to a new claim construction raised for the first time in the POR. *Axonics, Inc. v. Medtronic, Inc.*, 75 F.4th 1374, 1380 (Fed. Cir. 2023). Patent-Owner's expert (Dr. Mikos) identified four peaks in Dr. Simpson's alignment plot of Huang2 during his deposition. (EX1220, 109:11-110:14.) Applying Dr. Mikos's proposed arithmetic mean calculation to those identified peaks yields two peaks above the average, which would be considered "major peaks." (EX1219, ¶ 42.) Because those two peaks are separated by 180°, they satisfy the claims even under Patent-Owner's erroneous construction. (*Id.*)

D. A POSA Would Have Been Motivated to Use the Aligned fibers of Huang2 to Treat a Tendon, Ligament, or Nerve as Taught by Kuo

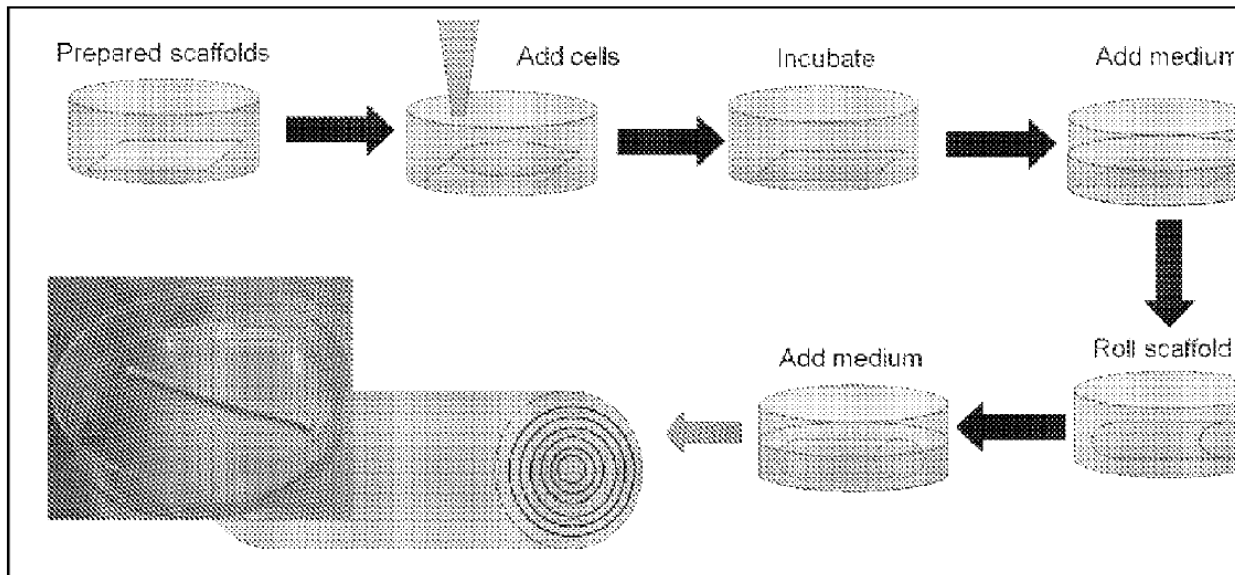
Patent-Owner argues that it would not have been obvious to use the aligned collagen blended fibers in Huang2 to treat “a tendon, ligament, or a nerve injury,” as recited in claim 1. But in so doing, the Patent-Owner mischaracterizes both Petitioner’s arguments and the references cited in the Petition.

1. Patent-Owner Mischaracterizes Kuo and the Arguments in the Petition

Patent-Owner argues that the Petition states that a POSA would use a scaffold comprising dermal fibroblasts, according to Huang2, and then use such a scaffold to treat a tendon, ligament, or nerve injury. (Paper-23, 36–37.) Patent-Owner provides a series of arguments for why this would not work and that there would thus be no motivation to combine Huang2 and Kuo. (*Id.*, 32–39; EX1219, ¶44.)

But Patent-Owner’s characterization of the Petition is not accurate. The Petition explains that “a POSA would have been motivated and able to use a scaffold comprising Huang2’s *aligned fibers*—as shown by FFT analysis—containing collagen, which may be cross-linked, to treat a tendon, ligament, or nerve defect *as taught by Kuo*.” (Paper-2, 30 (emphasis added).) This is correct based on the plain teaching of Kuo. (EX1219, ¶¶45-50.)

Kuo teaches a “schematic showing fabrication of a tissue construct.”



(EX1018, Fig. 1, [0022].)

The first step of the schematic, as shown in Fig. 1, is to start with a flat “scaffold sheet” of electrospun fibers, also referred to as a “mats.” (EX1018, [0005], [0007]; EX1220, 161:12-162:6; Paper-23, 39; EX1219, ¶46.)

In making the flat sheet, Kuo explains that “electrospinning can be performed by any means known in the art,” and states that “[e]lectrospinning for the formation of fine fibers has been actively explored recently for applications such as high performance filters and biomaterial scaffolds for cell growth, vascular grafts, *wound dressings* or *tissue engineering*.” (EX1018, [0040], [0046] (emphasis added).) Huang² is certainly in the field of tissue engineering, and Patent-Owner’s own expert characterizes Huang² as addressing “skin wo[und] repair.” (EX2015, ¶115.) Kuo thus provides the necessary motivation to look at the electrospinning

art in the tissue engineering and wound dressing space to find the best techniques to make highly aligned fibers. (EX1219, ¶¶47-48.)

Huang2's electrospinning techniques created highly aligned electrospun collagen-blended fibers, which is what Kuo teaches is preferred (EX1018, [0113-14]), and proved it using mechanical testing and FFT analysis, testing that is not present in Kuo. (EX1005, 1794; EX1003, ¶¶117-27; EX1220, 99:6-15, 102:1-16.) There would have been a reasonable expectation of creating the flat scaffold sheet as both Huang2 and Kuo were able to make such sheets. (Paper-2, 40-41.) Thus, there was motivation to use the flat sheet aligned scaffold of Huang2 as the first step of the Kuo schematic. (EX1219, ¶¶47-48.)

Kuo's second step is to seed the "[p]repared scaffolds" with cells, or as Fig. 1 states, "add cells." (EX1018, Fig. 1; EX1220, 161:20-22; EX1219, ¶49.) Thus, a POSA would take the flat sheet made by the techniques of Huang2 and, according to Kuo, seed it with "any cells . . . are found in the natural tissue to which the *construct is intended to correspond.*" (EX1018, [0058]; EX1219, ¶49.) Kuo then lists different cells that correspond to different tissues that can be repaired, such as a tendon or ligament. (*Id.*) Dr. Simpson stated that "a POSA would have been able to make and use a scaffold comprising Huang2's aligned fibers and *seeded with various cell types* using well-known established methods described in both Huang2 and Kuo." (EX1003, ¶102; EX1219, ¶49) Patent-Owner's assertions that one

would necessarily seed the scaffold made by the techniques of Huang2 with dermal fibroblasts to treat, for example, a tendon injury is not what Kuo teaches.

Kuo's third step is to take the electrospun collagen blended scaffold sheet, now seeded with the desired cells, and roll the sheets to approximate the structure of a tendon or ligament, or "[r]oll scaffold" as stated in Fig. 1. (EX1018, Fig. 1, [0022], [112], [115].) Thus, based 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. (EX1219, ¶50.)

2. Patent-Owner Mischaracterizes Huang2

Patent-Owner also argues that Huang2 discusses healing wounds to the skin and thus has no relevance to tendon or ligament repair, as taught by Kuo. (Paper-23, 36-39.)²

But the primary purpose of Huang2 was to investigate how the alignment of collagen fibers affects the differentiation of *fibroblasts* (which *are* discussed in

² It should be noted that Kuo specifically contemplates treating tissues that are made up of "keratinocytes" and "epithelial" cells, which are both found in the epidermis (EX1018, [0058]; EX1220, 166:4-168:16.)

Kuo) to myofibroblasts. (EX1005, Abstract, Decl., ¶¶; EX1220, 103:15-105:11; EX1018, [0058]; EX1219, ¶51.) The differentiation of fibroblasts to myofibroblasts is one of the essential healing pathways in treating many tissue injuries in the body, including tendon and ligament. (EX1219, ¶51; EX1220, 105:23-106:7.) Huang² found that aligned fibers promoted “fibroblast-to-myofibroblast differentiation” (EX1005, 1797; *see also* Paper-23, 11-12.)

Thus, a POSA would have understood that the teachings of Huang² have more applicability than treating skin wounds, and multiple teams have used “skin-derived fibroblasts” to treat tendon and ligament injuries. (*See* EX1206, 1-2, 8-10; EX1207, 901; EX1219, ¶¶52-56.) In EX1205, the authors used dermal fibroblasts to treat a tendon injury in an animal model, writing that that tenocytes and dermal fibroblasts exhibited “similar features,” including their “biomechanical” properties, “indicating that dermal fibroblasts may replace tenocytes for tendon engineering.” (EX1205, 786; EX1219, ¶54.)³ Thus, not only do both Huang² and Kuo discuss using blended collagen fibers to make scaffolds for injury repair, and also discuss the importance of the ECM, but both discuss the use of “fibroblasts,” which can be used to repair tissue injuries, such as a tendon or a ligament. (EX1219, ¶57.)

³ The '227 patent contemplates treating “an animal.” (EX1001, 18:54-57; EX1219, ¶54.)

3. Patent-Owner's Modulus Arguments Are Unsupported by the '227 Patent

Patent-Owner argues that a POSA would have been unable to use Huang2's scaffolds because its elastic modulus, stiffness, and degradation rate are insufficient. (Paper-23, 35–39.) But 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. *Uber Techn*, 957 F.3d at 1339; *In re Publicover*, 813 F. App'x 527, at 532; *Donghee Am.*, 2019 WL 80465, at *5. The '227 patent's teaching concerning treating an injury is prophetic and relies on the state of the art. (EX1220, 192:20-194:17.) The '227 patent makes no contribution above what was previously known. (EX1219, ¶¶43, 58.) Further, Patent-Owner's modulus argument is based on the false assumption that a POSA combining Huang2 and Kuo would use *only* dermal fibroblasts to treat a tendon injury. (Paper-23, 37–39.) As described above, that is not the case, and in any event, dermal fibroblasts were shown to treat a tendon injury. (EX1205, 783; EX1219, ¶¶52-56.) This same paper shows that the mechanical strength of the engineered tendon was sufficient and increased over time. (*Id.*, 786; EX1219, ¶59.)

E. It would have been Obvious in View of Huang2 and/or Kuo to Crosslink the Collagen Fibers

Patent-Owner also argues that there would have been no motivation to crosslink the collagen, as required by claim 1. But the '227 patent teaches that crosslinking was a “conventional” technique that therefore must be within the level of skill of a POSA. (EX1001 at 12:49-58; EX1219, ¶¶60-62.) Patent-Owner cannot contradict the teaching in its own patent. *See PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007). Consistent with 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. (See EX1005, 1791-92; Paper-13, 30-31; *see also* EX1219, ¶63.)

Further, the patent cites “glutaraldehyde” and “EDC” (EX1001, 12:49-58), which the prior art discloses as conventional crosslinking agents (EX1219, ¶61). Lee used glutaraldehyde to crosslink blended PCL/Collagen fibers to strengthen and increase the stability of the collagen. (EX1011, [0063]; EX1220, 186:19-188:10; EX1219, ¶63.) Kuo also teaches chemically crosslinking the electrospun fibers by incorporating Meinel, which crosslinked collagen fibers with EDC to avoid degradation. (EX1023, 380 (incorporated in its entirety into EX1018,

[0040]); EX1219, ¶63.)⁴ The literature cited by Patent-Owner also discusses crosslinking implants comprising PCL. (EX2018, 1230, 1240, 1243; EX1219, ¶63.)⁵

F. Dependent Claims 2-6 Would Have Been Obvious

Claim 2 requires the scaffold to be “one or more elongated sheets.” (EX1001, Claim 2.) Kuo begins with a flat “sheet.” (EX1018, Fig. 1, Claim 1; EX1220, 161:12-162:13; EX1219, ¶65.) Because claim 2 uses the open-ended transition “comprising,” Kuo’s additional rolling step does not remove it from the claim’s scope. A rolled sheet is still a sheet, and Kuo’s use of multiple rolled sheets renders claim 2—and claim 3’s “multiple layers of one or more sheets”—obvious. (EX1219, ¶¶65-66.) This is confirmed by the ’227 patent, which discusses “folding

⁴ Patent-Owner argues that Meinel should be disregarded because it only crosslinked pure collagen fibers. (Paper-23, 16.) But Kuo itself disclosed blended PCL/collagen fibers (EX1018, [0113]), and the claims themselves are not limited to blended collagen.

⁵ Contrary to Patent-Owner’s assertions (Paper-23, 15-16 (citing EX2020)), Dr. Simpson’s paper supports, rather than undermines, crosslinking by confirming its necessity for scaffold integrity and noting that cytotoxicity can be addressed through known agents and techniques. (*See also* EX2017, 189:5-8; EX1219, ¶64.)

or rolling the sheet.” (EX1001, 8:40-43.) Kuo also broadly discloses scaffolds as “films” or “sheets,” and the prior art, including Dr. Mikos’s work, demonstrates the advantages and motivation for multilayer sheets. (EX1018, [0024]; EX1219, ¶65, 67; EX1220, 146:14-22, 148:20-150:12; EX1209, 1206.)

Claims 4, 5, and 6 require treating nerve, ligament, and tendon, respectively. As discussed in the Petition and above (Paper-2, 28–30, 39–41, 43–46; *see also* EX1219, ¶68), a POSA would have been motivated to combine Huang² and Kuo to treat those tissues.

G. Lee Alone or in Combination with Kuo Render Claims 1-6 Obvious

1. Lee’s Highly Aligned Fibers Have the Peaks Recited in Claim 1

The Petition argues that Lee discloses this element to a POSA by disclosing aligned fibers, which by definition, must have two major peaks in the FFT 180° from each other. The Petition argues that “Lee by itself also discloses this element of the claim by describing aligned PCL/collagen fibers. (Paper-2, 47 (citing EX1003).) EX1003 is the declaration of Dr. Simpson, who expands upon the point, explaining that “an FFT analysis measures the degree of fiber alignment, and an FFT result showing fibers having adjacent major peaks with about 180° apart from each other *only occurs when the fibers are aligned.*” (See EX1003, §VI.B.1.c, ¶176 (emphasis added).) Indeed, it was well-known in the prior art, as published by

Ayres2008, which has been cited hundreds of times, that “scaffolds containing aligned elements exhibit . . . two larger peaks at 90° and 270°,” which are 180° apart. (EX1010, 610; EX1219, ¶¶69-73; Paper-2, 8 (citing EX1010).) Patent-Owner also acknowledges this in its POR. (Paper-23, 4 (citing EX1010, 610).) The Petition then discusses the evidence demonstrating that Lee obtained highly aligned collagen blended fibers, including fiber orientation testing using computer analysis and mechanical testing. (Paper-2, 48–50.)

This is sufficient to establish that Lee discloses the claimed FFT element. As mentioned above, the Patent-Owner at the district court argued that “highly aligned” fibers fall within the claims. (EX2005, ¶59.) “[I]t is axiomatic that that which would literally infringe if later anticipates if earlier.” *Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001).

Patent-Owner argues that Dr. Simpson’s testing shows that the peaks are there inherently and that since inherency was not raised, the Board can ignore Dr. Simpson’s testing. (Paper-23, 42–43.) Inherency, however, typically examines whether properties that are *unknown* and *not recognized* by a POSA in the prior art are nevertheless there. *Honeywell International Inc. v. Mexichem Amanco Holding SA DE CV*, 865 F.3d 1348, 1354 (Fed. Cir. 2017). As a POSA of the priority date for the ’227 patent would have known and understood that Lee’s highly aligned

fibers have the necessary FFT peaks, Petitioner argued, as set forth above, that Lee discloses to a POSA the required peaks by describing highly aligned fibers.

Indeed, the Board specifically found in *AMCOL Int'l Corp. v. Oil-Dri Corp. of Am.*, IPR2022-01107, 2023 WL 8264190, at *9-10 (P.T.A.B. Nov. 29, 2023), that “[w]e do not see the bright line distinction between Petitioner’s approach [what a POSA would “understand” from the prior art] and the inherency standard that Patent-Owner suggests because, as Petitioner asserts, the same evidence can satisfy both standards.” *Id.*

Moreover, the Petition specifically asserts inherency. 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).) Thus, whether the

Board finds that a POSA would understand that the requisite peaks are there because of the testing performed in Lee to show alignment or that the peaks are “inherently” there, the result is the same.

Moreover, Patent-Owner’s criticisms of Dr. Simpson’s testing are recycled from its arguments concerning Huang², and Petitioner’s response above apply equally here. (Paper-23, 43–55; *see* § II.B., *supra*; EX1219, ¶¶74-75.) In particular, Dr. Simpson has shown that large amounts of noise do prevent an FFT of aligned fibers from demonstrating the claimed FFT peaks. (EX1219, ¶75.)

Finally, the Petition also argued a POSA “would have been motivated” to use FFT to confirm that orientation of the fibers and would have a reasonable expectation of success in doing so. (Paper-2, 51.) Patent-Owner argues that there would have been no motivation to run an FFT because Lee already confirmed that alignment. (Paper-23, 46–48.) But in advancing this argument, Patent-Owner ignores that the techniques used in Lee (analysis of an SEM image and mechanical testing) are *destructive* of the scaffold just created. (EX1220, 54:5-8, 56:13-57:9; EX1219, ¶73.) One of the advantages pointed out by Dr. Simpson of the FFT technique he developed is that it is *non-destructive*. (EX1003, ¶11; EX1220, 55:5-17; EX1219, ¶73.) Thus, if a POSA wanted to follow Lee to engineer a scaffold to treat a tissue, and wanted to confirm the fibers are in fact aligned, then FFT would have been used as it is a simple, non-destructive technique, that can be used on a

brightfield microscope image of the scaffold, and the scaffold can be subsequently used to treat the injury. (EX1219, ¶73; EX1010, 620.)

2. A POSA Would Have Been Motivated to Use Lee's Scaffold to Treat a Tendon, Ligament, or Nerve

Contrary to Patent-Owner's assertions, a POSA would have been motivated, at the very least, to combine Lee and Kuo to treat a tendon, ligament, or nerve, because, as noted by the Board, both Lee and Kuo teach scaffolds that can be used to treat muscle injuries and given that both references disclose treating a common tissue, there was a motivation to combine. (Paper-13, 40; *see also* Paper-2, 51–54; EX1219, ¶¶76-81.) Further, the reasons discussed above in the context of Huang² concerning all the teachings of Kuo, would apply equally to Lee., and Patent-Owner's challenges related to elastic modulus, stiffness, and degradation, fail for the same reasons. (EX1219, ¶¶78-81; *see* II.D.3, § *supra*.)

3. Dependent Claims 2-6 Would Have Been Obvious

Lee's electrospun fibers would constitute a sheet (as called for by claim 2), and Lee itself states that the sheets can be in multiple layers (as called for by claim 3). (*See* EX1003, ¶208; Paper-2, 54–55; EX1219, ¶¶82-83.) Moreover, Kuo also discloses this limitation, as set forth above. (*See* §II.F., *supra*.)

Claims 4, 5, and 6 require treating nerve, ligament, and tendon, respectively. As discussed in the Petition and above (Paper-2, 45–54, 56–59; *see* §II.D, *supra*;

EX1219, ¶84), a POSA would have been motivated to treat these tissues with Lee's scaffold in view of Lee alone or Lee in view of Kuo.

H. Huang2 Anticipates Claims 7-8

Patent-Owner's response to these claims is that Huang2 lack the requisite peaks. Patent-Owner is wrong for all the reasons set forth above.

III. CONCLUSION

Petitioners respectfully submit that the challenged claims are unpatentable.

Respectfully submitted,

Dated: February 4, 2026

By: /Howard W. Levine/
Howard W. Levine (Reg. No. 41,453)

CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that the foregoing **Reply to Patent-Owner's Response** contains 5587 words, as measured by the word-processing system used to prepare this paper.

Dated: February 4, 2026

By: /Howard Levine/
Howard Levine (Reg. No. 41,453)

CERTIFICATE OF SERVICE

I hereby certify that on February 4, 2026, I caused a true and correct copy of the forgoing Reply to Patent-Owner's Response to be served via electronic upon to the Patent-Owner's counsel of record at the following addresses:

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