

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.

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

PATENT OWNER'S RESPONSE
37 C.F.R. § 42.120

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LIST OF EXHIBITS

Patent Owner’s Exhibits

Exhibit Number	Description
2001	U.S. Patent Application Publication No. 2012/0221025, published Aug. 30, 2012 (“Simpson”)
2002	WO 2012/078472, published June 14, 2012 (“Patel”)
2003	Dorland’s Illustrated Medical Dictionary (29th ed. 2000) – “progenitor”
2004	Dorland’s Illustrated Medical Dictionary (29th ed. 2000) – “stem c[ell]”
2005	First Amended Complaint, <i>LifeNet Health v. Zimmer Biomet Holdings, Inc., et al.</i> (E.D. Va. 2:23-cv-479)
2006	Exhibit N to the First Amended Complaint, <i>LifeNet Health v. Zimmer Biomet Holdings, Inc., et al.</i> (E.D. Va. 2:23-cv-479)
2007	Exhibit O to the First Amended Complaint, <i>LifeNet Health v. Zimmer Biomet Holdings, Inc., et al.</i> (E.D. Va. 2:23-cv-479)
2008	Patent Owner’s Proposed Discovery Requests
2009	Webpage, Tapestry® Biointegrative Implant (https://www.zimmerbiomet.com/en/products-and-solutions/specialties/sports-medicine/tapestry-biointegrative-implant.html#06-related-product)
2010	Webpage, Tapestry® RC Biointegrative Implant System (https://www.zimmerbiomet.com/en/products-and-solutions/specialties/sports-medicine/tapestry-rc-biointegrative-implant-system.html)

2011	Webpage, ActivBraid® Collagen Co-Braid (https://www.zimmerbiomet.com/en/products-and-solutions/specialties/sports-medicine/activbraid.html)
2012	Presentation by Jeff Conroy, CEO, Embody, LSI USA '22 Emerging Medtech Summit
2013	Press Release dated January 5, 2023, “Zimmer Biomet to Acquire Embody, Inc.”
2014	Webpage, Wayback Machine, Our Technology - Embody (https://web.archive.org/web/20250512015553/https://embody-inc.com/our-technology/)
2015	Declaration of Dr. Antonios G. Mikos, Ph.D. in Support of Patent Owner’s Response
2016	<i>Curriculum Vitae</i> of Dr. Antonios G. Mikos, Ph.D.
2017	Transcript of October 7, 2025 Deposition of Dr. David Simpson
2018	Woodruff et al., <i>The return of a forgotten polymer- Polycaprolactone in the 21st century</i> , 35 Progress in Polymer Science 1217-1256 (2010) (“Woodruff”)
2019	Zeugolis et al., <i>Electro-spinning of pure collagen nano-fibres — Just an expensive way to make gelatin?</i> , 29 Biomaterials 2293-2305 (2008) (“Zeugolis”)
2020	Barnes et al., <i>Cross-Linking Electrospun Type II Collagen Tissue Engineering Scaffolds with Carbodiimide in Ethanol</i> , Tissue Engineering (Vol. 13) 1593-1605 (2007) (“Barnes”)
2021	Rothamel et al., <i>Biodegradation of differently crosslinked collagen membranes: an experimental study in the rat</i> , 16 Clin. Oral Impl. Res. 369-378 (2005) (“Rothamel”)
2022	U.S. Patent No. 9,572,909 to Simpson, et al., entitled “Electrospun nerve guides for nerve regeneration designed to modulate nerve architecture”

2023	Sikavitsas, et al., <i>Formation of three-dimensional cell/polymer constructs for bone tissue engineering in a spinner flask and a rotating wall vessel bioreactor</i> , J. Biomed. Mater. Res., 62, 136-148 (2002) (“Sikavitsas”)
2024	Engler, et al., <i>Matrix elasticity directs stem cell lineage specification</i> , Cell 126, 677-689 (2006) (“Engler”)
2025	Gennison, et al., <i>Human muscle hardness assessment during incremental isometric contraction using transient elastography</i> , 38 J. Biomechanics, 1543-1550 (2005) (“Gennison”)
2026	Johnson, et al., <i>Tensile and Viscoelastic Properties of Human Patellar Tendon</i> , J. of Orthopaedic Research, 796-803 (1994) (“Johnson”)
2027	Hashemi, et al., <i>The mechanical properties of human patellar tendon are correlated to its mass density and are independent of sex</i> , 20 Chemical Biomechanics, 645-652 (2005) (“Hashemi”)
2028	Butler, et al., <i>Comparison of Material Properties in Fascicle-Bone Unites from Human Patellar Tendon and Knee Ligaments</i> , 19 J. Biomechanics, 425-432 (1986) (“Butler 1986”)
2029	Butler, et al., <i>Location-Dependent Variations in the Material Properties of the Anterior Cruciate Ligament</i> , 25 J. Biomechanics, 511-518 (1992) (“Butler 1992”)
2030	Ma, et al., <i>In vitro and in vivo mechanical properties of human ulnar and median nerves</i> , J Biomed Mater Res Part A 2013:101A:2718–2725 (“Ma”)
2031	Ni Annaidh, et al., <i>Characterization of the anisotropic mechanical properties of excised human skin</i> , J. Mech. Behavior of Biomedical Materials, 139-148 (2012) (“Ni”)
2032	Attorney’s Illustrated Medical Dictionary (1997) – “sheet”
2033	Dorland’s Illustrated Medical Dictionary (29th ed. 2000) – “sheet”

2034	Crisan, et al., <i>A Perivascular Origin for Mesenchymal Stem Cells in Multiple Human Organs</i> , Cell Stem Cell 3, 301-313 (2008) (“Crisan”)
2035	Lustig, et al., <i>Solute Diffusion in Swollen Membranes, IX. Scaling Laws for Solute Diffusion in Gels</i> , 36 J. Applied Polymer Science, 735-747 (1988) (“Lustig”)

I. INTRODUCTION

Patent Owner LifeNet Health (“LifeNet” or “Patent Owner”) submits this Response to the Petition filed by Embody. Inc. and Zimmer Biomet Holdings, Inc. (“Petitioner”), challenging claims 1-8 of U.S. Patent Number 11,318,227 (“the ’227 patent”). Paper 2 (“Petition” or “Pet.”). The Patent Trial and Appeal Board (“PTAB” or “Board”) instituted review of the Petition on August 5, 2025. Paper 13 (“Decision on Institution” or “DI”).

Petitioner falls far short of meeting its burden to demonstrate unpatentability by a preponderance of the evidence. To the contrary, none of Petitioner’s cited references disclose or suggest certain elements of the claims. Among other deficiencies, Petitioner’s Huang2 reference lacks “major ... peaks” which, as properly construed, require “a height higher than the average height of the peaks in the result.” Petitioner’s alternate reliance on its expert’s post-hoc testing of a photocopy of Huang2’s image does not cure this deficiency because that testing flatly contradicts Huang2 and warrants no weight. Nor does Petitioner demonstrate that a skilled artisan would have modified Huang2 to crosslink its blended fibers or to repair different tissue types.

The Petition fares no better with Lee. Petitioner fails to specifically identify any theory of unpatentability with reasonable particularity. As preliminarily noted in the Decision on Institution, “Petitioner does not clearly assert ... that the fibers

taught by Lee necessarily or inherently satisfy the FFT analysis requirement.” DI 36 (“Petitioner’s grounds based on Lee may ultimately fail on the merits due to this lack of specificity.”). Moreover, Petitioner again fails to demonstrate that a skilled artisan would have used Lee to repair tendon, ligament, or nerve tissue where such repair requires a scaffold with a three-dimensional rolled structure, a vastly different elastic modulus and scaffold structure, and entirely different seeded cells than those disclosed by Lee.

For the reasons set forth in detail below, Petitioner fails to demonstrate by a preponderance of the evidence that claims 1-8 are unpatentable.

II. THE ’227 PATENT

A. The ’227 Patent

1. A scaffold comprising electrospun fibers

The ’227 patent discloses a “scaffold comprising an aligned fiber.” Ex. 1001, Abstract, 13:23- 29. This scaffold may facilitate growth of, e.g., bone, ligament, or tendon, *id.* at 11:28-57, and may be incorporated into biocompatible implants to repair or restore tissues damaged by disease or trauma. *Id.* at 16:18-20. “The invention also relates to methods of treating a tissue ... comprising administering ... the aligned fiber, electrospun fiber, scaffold and/or implant described herein to the tissue” *Id.* at 18:54-62.

Scaffolds comprising aligned fibers may be formed by electrospinning and may be “as small as one nanometer.” *Id.* at 13:23-25, 2:42-44. The ’227 patent

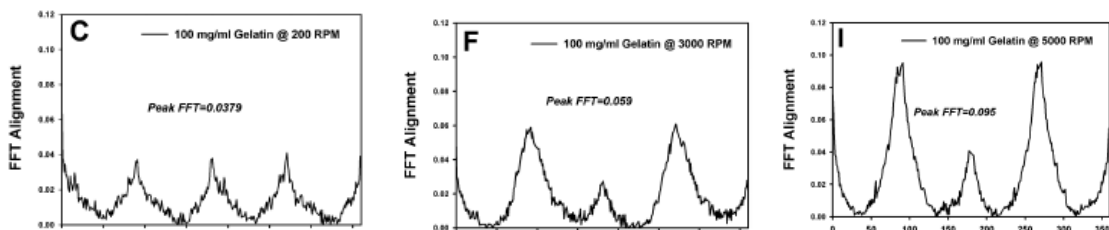
discloses electrospun fibers aligned in one direction and formed into an elongated roll or sheet, a composite of multiple layers of sheets, or a combination. *Id.* at 8:26-35. These scaffolds may comprise collagen. *Id.* at 13:50-14:2. In some embodiments, the fibers may be crosslinked. *Id.* at 13:49-52.

2. Fast Fourier transform analysis

To measure fiber alignment, the '227 patent employs fast Fourier transform (“FFT”) analysis. *Id.* at 13:38-49. The '227 patent incorporates a 2008 publication, to which Petitioner’s declarant Dr. David G. Simpson is the senior author, further describing FFT analysis. *Id.*; Pet. 11; Ex. 1003 ¶ 62.

Dr. Simpson’s 2008 paper uses FFT analysis “to measure fiber alignment in electrospun materials.” Ex. 1010, Abstract. “The 2D FFT function converts spatial information in an optical data image into a mathematically defined frequency domain,” which “maps the rate at which pixel intensities change in the spatial domain.” *Id.* at 608.

The paper provides three examples of FFT analysis results, plotted on a scale from 0 to 360°, and shown below.



Ex. 1010, 608 at Figs. 1C, 1F, 1I. The 2008 paper explains that a FFT analysis result for “a random matrix [of fibers] will exhibit 4 peaks that occur every 90°. Peaks of nearly uniform height are a hallmark of a scaffold composed of random elements.” *Id.* at 609, Fig. 1C. By contrast, “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.

A FFT analysis result conveys information about the analyzed fibers. For example, “the height and overall shape of the most prominent peaks present in the alignment plot” conveys “[t]he degree of alignment present in the original data image”; the shape of the peak conveys the uniformity of alignment, where “[a] high and narrow peak indicates a more uniform degree of fiber alignment, [but] a broad peak, or a shoulder on the peak indicates that more than one axis of alignment may be present”; and, finally, “the principal axis of fiber alignment is determined by the position of the alignment peaks.” *Id.* (emphases added); Ex. 1003 ¶¶ 41-42.

The '227 patent explains that the FFT analysis result of the claimed scaffold shows “adjacent major peaks with about 180° apart from each other,” where “major peaks” “refer to peaks higher than the average of the peaks in the result.” Ex. 1001, 13:25-29. This is depicted in Figure 8A, reproduced below alongside Figure 8B.

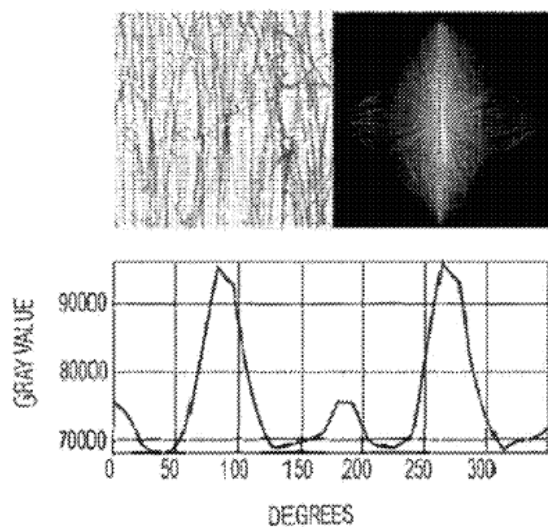


FIG. 8A

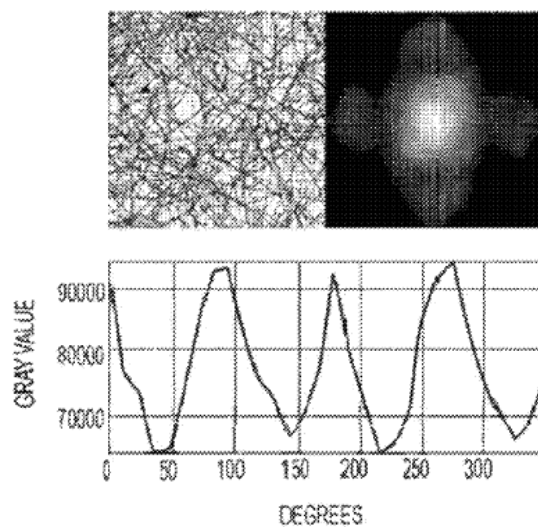


FIG. 8B

Id. at 13:46-49, Figs. 8A-8B. “FIG. 8A depicts exemplary FFT analysis results of the fibers described herein ... Fig. 8B depicts an FFT analysis of a control sample.”

Id. at 2:10-12. As shown, aligned fibers show adjacent major peaks with about 180° apart from each other (Figure 8A), while non-aligned fibers do not (Figure 8B). *Id.* at 13:46-49.

3. Cell seeding

Specific cells may be seeded and cultured on the scaffold to repair specific tissues. *Id.* at 10:56-57, 16:26-27. In some embodiments, stem cells are used. *Id.* at 16:27-30. The “differentiation of stem cells into osteoblasts, chondrocytes, ligament or tendon” is promoted by “culturing the cells on the scaffold or aligned fiber described herein in conditions suitable for the cell differentiation.” *Id.* at 1:31-35, 16:54-18:17.

B. The '227 Patent Claims

Claims 1-8 are challenged. Pet. 1. Claims 1 and 7 are independent and recite:

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.

III. LEVEL OF SKILL IN THE ART

Patent Owner generally does not dispute Petitioner's identified level of skill possessed by a person of ordinary skill in the art ("POSITA"), however, Patent Owner clarifies that a POSITA would have earned their Ph.D. in bioengineering, chemical engineering, mechanical engineering, or a related engineering discipline. Pet. 20-21; Ex. 2015 ¶ 39. Patent Owner's declarant, Dr. Mikos, meets both Petitioner's and Patent Owner's definition. Ex. 2015 ¶ 40.

IV. CLAIM CONSTRUCTION

Claim construction is necessary here. *Contra* Pet. 21.

Independent claims 1 and 7 recite: “major adjacent peaks.” Ex. 1001, 23:34-35, 24:8. Here, the patentee provided an express definition of “major peaks” in the ’227 patent: “‘major peaks’ herein refer to peaks higher than the average of the peaks in the result.” *Id.* at 13:28-29.

A patentee may “be his own lexicographer ... 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). To determine whether a term is definitional, “the intrinsic evidence must ‘clearly set forth’ or ‘clearly redefine’ a claim term so as to put [a POSITA] on notice that the patentee intended to so redefine the claim term.” *Bell Atlantic Network Servs., Inc. v. Covad Comms. Grp., Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001) (citation omitted)

Here, the ’227 patent’s Specification clearly meets this definitional standard. Ex. 1001, 13:28-29. In particular, the term “major peaks” “is set off in quotation marks,” indicating that it is definitional. *Alnylam Pharms., Inc. v. Moderna, Inc.*, 138 F.4th 1326, 1333 (Fed. Cir. 2025). The definitional sentence also uses “‘refer to,’ which generally conveys an intent for [that sentence] to be definitional.” *Id.* Further, this language is unqualified and does not use “non-limiting terms” that detract from its definitional nature, such as “e.g.” or “for example.” *Id.*

Finally, although “it is ... improper to limit the claims to the particular preferred embodiments ..., the patentee’s choice of preferred embodiments can shed

light on the intended scope of the claims.” *Astrazeneca AB v. Mut. Pharm. Co.*, 384 F.3d 1333, 1340 (Fed. Cir. 2004). Here, the only disclosed embodiment of “major peaks” is shown in Figure 8A below and matches the Specification’s express definition.

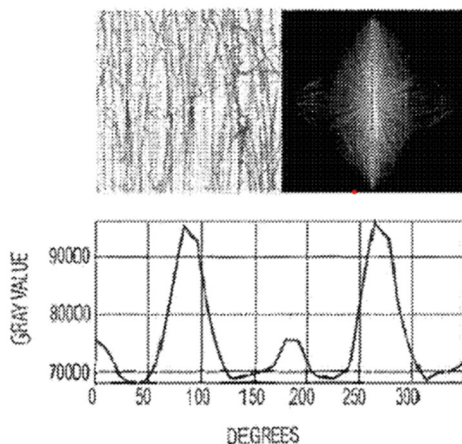


FIG. 8A

Ex. 1001, Fig. 8A, 13:46-48. As shown in Figure 8A, the peaks that occur at 90° and 270° are “major peaks” as defined. Indeed, their height is higher—peaking at approximately 95,000 units—than the average height of the four peaks shown in the result. Ex. 2015 ¶ 57 (explaining that four peaks are depicted in the result with those at 0° and 180° having a height of 95,000, and those at 90° and 270° having a height of 75,000, such that the average is approximately 85,000 units).

Dr. Mikos testifies that the Specification’s definition of “major peaks” is consistent with how a POSITA would have understood the term. Ex. 2015 ¶ 58. Dr. Mikos explains that the “FFT process plots the high frequency signals in the

image, which reflect fiber alignment, as prominent or ‘major’ peaks that depict the extent of fiber alignment.” *Id.* (citing Ex. 1010, 610). Those are necessarily higher than the average heights of all peaks in the FFT result because the FFT analysis will also depict smaller peaks which reflect lower frequency signals. *Id.* ¶ 59.

During his deposition, Dr. Simpson agreed that a “way to describe a major peak [would] be that its height is higher than the average heights of the peaks in the plot.” Ex. 2017, 89:3-9 (agreeing that “major” is a relative term). This is consistent with his prior statements. Ex. 1010, 610 (explaining that the “degree of alignment ... is reflected by the height and overall shape of the most prominent peaks”), 615 (“The larger peaks report the principle axis of alignment while the smaller peaks correspond to background information, noise and edge effects.”); Ex. 1003 ¶¶ 40-41.

Here, the patentee acted as lexicographer and presented a clear definition of “major peaks.” This definition aligns with the disclosed embodiments and with understanding of a POSITA. Ex. 2015 ¶¶ 58-59; Ex. 2017, 89:3-9. Accordingly, the claim should be construed as “major adjacent peaks that are about 180° apart from each other where each major peak has a height higher than the average height of the peaks in the result.”

V. PETITIONER FAILS TO PROVE UNPATENTABILITY BY A PREPONDERANCE OF THE EVIDENCE

A. The Asserted Grounds and Prior Art

Petitioner presents the following grounds. Pet. 4.

Claim(s) Challenged	35 U.S.C.	Reference(s)
1-6	§ 103	Huang2 ¹ , Kuo ²
1-6	§ 103	Lee, ³ Kou
7-8	§ 102	Huang2

1. Huang2

Huang2 discloses an electrospun skin-repair scaffold made from a blend of collagen and polycaprolactone (“PCL”). Ex. 1005, 1791. “To better support and facilitate skin cells to form skin-like tissues, it is necessary for the temporary scaffolds ... to define a cell-friendly microenvironment that maximally recaptures

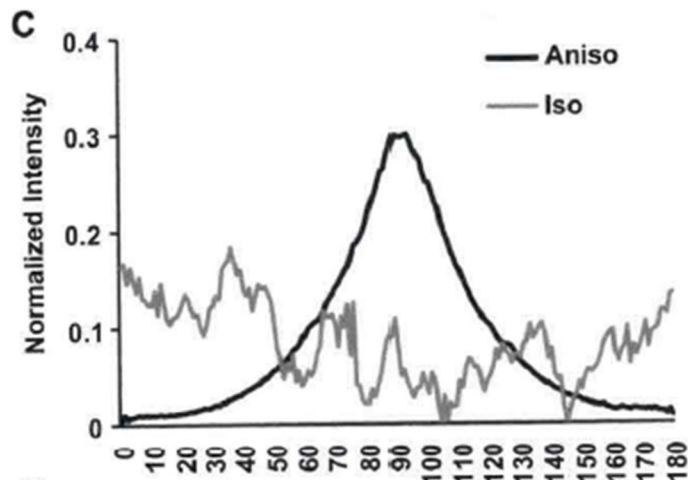
¹ Huang et al., *The involvement of integrin $\beta 1$ signaling in the migration and myofibroblastic differentiation of skin fibroblasts on anisotropic collagen-containing nanofibers*, 33 BIOMATERIALS 1791–1800 (2012) (“Huang2,” Ex. 1005).

² Kuo, U.S. Patent Application Publication No. 2011/0293685 A1, published Dec. 1, 2011 (“Kuo,” Ex. 1018).

³ Lee et al., U.S. Patent Application Publication No. US 2010/0331980 A1, published Dec. 30, 2010 (“Lee,” Ex. 1011).

the native extracellular matrix.” *Id.*

Huang2 discloses that “[t]he orientation of electrospun nanofibers was determined by using the ImageJ program (NIH) along with the Oval Profile Plot plugin.... These cropped images were then processed with” FFT. *Id.* at 1792. Huang2’s Figure 1C is reproduced below.



Huang2’s Figure 1C depicts “[n]ormalized intensity plots against the angle of acquisition for isotropic and anisotropic nanofibrous matrices,” where aligned fibers present a single peak.⁴ *Id.* at 1793. Huang2 explains that “[t]he narrow peak ... indicated that PCL/Coll nanofibers aligned along a single axis.” *Id.* at 1794.

To facilitate skin repair, normal human dermal fibroblasts (“NHDF”) are

⁴ Huang2 defines “isotropic” as “fibers collected randomly with no alignment” and “anisotropic” as “fibers collected with alignment.” Ex. 1005, Abstract.

seeded and cultured on the nanofibrous matrices, which resulted in “elongated cell morphology, distinct distribution of focal adhesions, accelerated cell migration and promoted fibroblast-to-myofibroblast differentiation.” *Id.* at 1792, 1799.

2. Lee

Lee discloses muscle-repair scaffolds. Ex. 1011, Abstract. Lee explains that “it is preferable to mimic native skeletal muscle construction, with its highly-oriented fibers of fused mononucleated muscle cells.” *Id.* ¶ 4. Lee’s scaffold may comprise electrospun collagen, optionally with polymers like PCL. *Id.* ¶ 6.

Human skeletal muscle cells (“hSkMCs”) are seeded on Lee’s scaffold. *Id.* ¶¶ 60, 72-73. After being cultured, “[t]he cells fused and formed myotubes.” *Id.* ¶ 82.

3. Kuo

Kuo discloses scaffolds for various types of “tissue regeneration, enhancement, or tissue repair.” Ex. 1018, Abstract. Electrospun fiber mats “can be seeded with cells and subsequently rolled into a desired shape/form to replace a desired tissue.” *Id.* Kuo teaches repair of various tissue types depending upon the cell type seeded on the scaffold. *Id.* ¶ 58 (“[D]ifferent cell types or combinations thereof may be employed ... depending upon the intended function of the tissue engineered construct being produced.”). For example, Kuo repairs ligament, tendon, nerve, cardiac muscle, and skeletal muscle, among other tissues. *Id.* ¶¶ 52, 67-68.

Kuo's scaffolds are "subsequently rolled into cylindrical form" to form a "spirally wound tissue construct." *Id.* ¶¶ 5, 20, 22. Kuo states that this rolled structure "locally mimic[s] the native microstructure of tendon/ligament (aligned collagen fibrils), globally mimic[s] a fascicle or bundle in tendon/ligament tissue, and result[s] in cell seeding throughout the construct," thus avoiding the "poor cell seeding ... that is a major limitation of aligned scaffolds due to their low porosity as a result of closely packed aligned fibers." *Id.* ¶ 112.

B. Ground 1: Huang2 and Kuo do not render claims 1-6 obvious

1. Huang2 lacks "crosslinked fibers"

Claim 1 requires "crosslinked fibers comprising collagen." Ex. 1001, 23:31-32. Although Huang2 discloses crosslinking as one possible way to obtain a stable scaffold, *Huang2 does not employ crosslinking*. Instead, Huang2 blends polycaprolactone (PCL) with collagen to achieve stability. Ex. 1005, 1791 ("[E]ither crosslinking or combination with other materials is necessary to obtain a stable scaffold."), 1792 (3:1 blend). Dr. Mikos testifies that these are alternative ways to achieve stability. Ex. 2015 ¶ 64 (explaining that a POSITA would have weighed factors of each).

The Petition does not suggest—let alone demonstrate—that Huang2's blended fibers are insufficiently stable such that a POSITA would additionally crosslink those fibers. To the contrary, by blending PCL and collagen in a 3:1 ratio,

Huang2 already achieved the stability needed for its scaffold. *Id.* ¶ 65 (“Huang2 achieved a very stable compound.”); Ex. 1005, 1791 (“Electrospinning a blend solution of collagen and polycaprolactone (PCL) ... can yield rather stable nano fibers.”). In fact, PCL degrades much more slowly than collagen with PCL degrading over years as compared to weeks to months for collagen. Ex. 2018, Abstract (identifying “long-term degradation (up to 3-4 years)” for PCL); Ex. 2021, 376 (identifying degradation of as little as 2 weeks for non-crosslinked to as much as > 24 weeks for crosslinked collagen); Ex. 2015 ¶ 65 (explaining that as hydrophilic crosslinked collagen absorbs water it necessarily degrades more quickly than Huang2’s hydrophobic PCL/collagen blend).

Dr. Simpson agrees that PCL denatures more slowly than collagen. Ex. 2017, 180:16-181:4. In fact, Dr. Simpson testified that a PCL/collagen blend, like Huang2’s, will dissolve at a rate approximating that of PCL, which is much slower than collagen. Ex. 2017, 184:21-185:1; Ex. 2015 ¶ 65; Ex. 2018, Abstract; Ex. 2021, 376. Accordingly, Huang2’s blend possesses sufficient stability. Ex. 2015 ¶ 65.

What is more, crosslinking Huang2’s blended scaffold would impose unnecessary disadvantages without appreciable benefit. For example, Dr. Mikos testifies that crosslinking would add cost to scaffold fabrication. *Id.* ¶ 67. Crosslinking would also strip away collagen’s known benefits, such as enhanced biocompatibility. *Id.* ¶ 68. And crosslinking would raise toxicity concerns. *Id.* A

POSITA would not further crosslink Huang2's already stable scaffold in the face of these disadvantages. *Id.* ¶ 71.

Dr. Simpson recognizes these risks. For example, Dr. Simpson previously published that “[c]ross-linking ... may compromise biocompatibility” and risks “los[ing] the[] nanofibrous morphology, which is one of the most important features of the [electrospun collagen] scaffold to begin with.” Ex. 2020, 1594. It goes without saying that biocompatibility is important for an implantable tissue scaffold. Ex. 2017, 187:12-16.

Many popular crosslinking agents are also “cytotoxic because of the reactive moieties that are covalently coupled between neighboring collagen fibrils.” Ex. 2020, 1594. Cytotoxicity is problematic for an implantable tissue scaffold. Ex. 2017, 188:24-189:8. Moreover, glutaraldehyde, “the most commonly used and accepted agent for the cross-linking of biological tissues,” has been “implicated in the development of calcification.” Ex. 2020, 1594. Calcification poses a problem for scaffolds like those claimed in the '227 patent, which are designed to repair tendons, ligaments, and nerves, because calcification imparts detrimental rigidity to the scaffold. Ex. 2015 ¶ 68; Ex. 2017, 189:25-192:15 (explaining that calcification “would probably reduce the elasticity, and that might cause a problem” for specific tissues).

A POSITA would not have further crosslinked Huang2's blended fibers in the

face of these well-documented disadvantages and certainly would not have done so absent a reason to believe Huang2's scaffold was insufficiently stable. In fact, Dr. Simpson's own laboratory successfully utilized "blends of collagen with synthetic polymers" specifically "[t]o avoid" crosslinking's disadvantages. Ex. 2020, 1594.

Petitioner's reliance on Meniel is inapposite because Meniel crosslinked *pure* collagen. Ex. 1023, 380-381; Ex. 2015 ¶ 70. Meniel does not crosslink a stable PCL/collagen blend like Huang2. Ex. 2015 ¶ 70.

In sum, Petitioner's conclusion that a POSITA would have crosslinked Huang2's blended scaffold to "improve the stability" is insufficiently supported. Pet. 33-34; Ex. 2015 ¶ 70. Nor does Petitioner demonstrate that a POSITA would have accepted the known disadvantages of crosslinking to do so.⁵ Ex. 2015 ¶ 71; *Edwards Lifesciences v. Aortic Innovations LLC*, IPR2023-01232, Paper 10 at 36-37 (finding the purported motivation "inchoate" and "unpersuasive" because the "benefits" of the combination "are already conferred"); *UiPath, Inc. v. Rule 14 LLC*,

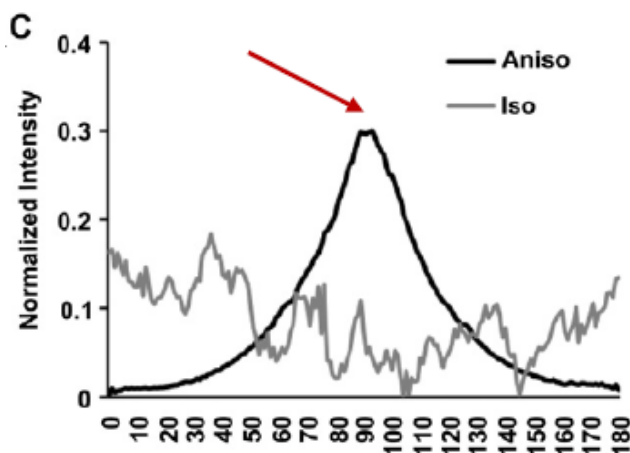
⁵ As a practical matter, crosslinking blended PCL/collagen fibers is difficult because the PCL slows the diffusion of aqueous crosslinkers into the fibers due to its hydrophobicity. Ex. 2015 ¶ 69; Ex. 2035, 745.

IPR2024-01304, Paper 8 at 26-27 (PTAB Mar. 14, 2025) (finding no motivation where the primary reference “already includes” the purportedly motivating feature).

2. Huang2 lacks “major ... peaks”

Properly construed, the “major ... peaks” recited in claim 1 require “a height higher than the average height of the peaks in the result.” *Supra* § IV. Huang2 does not disclose this limitation.

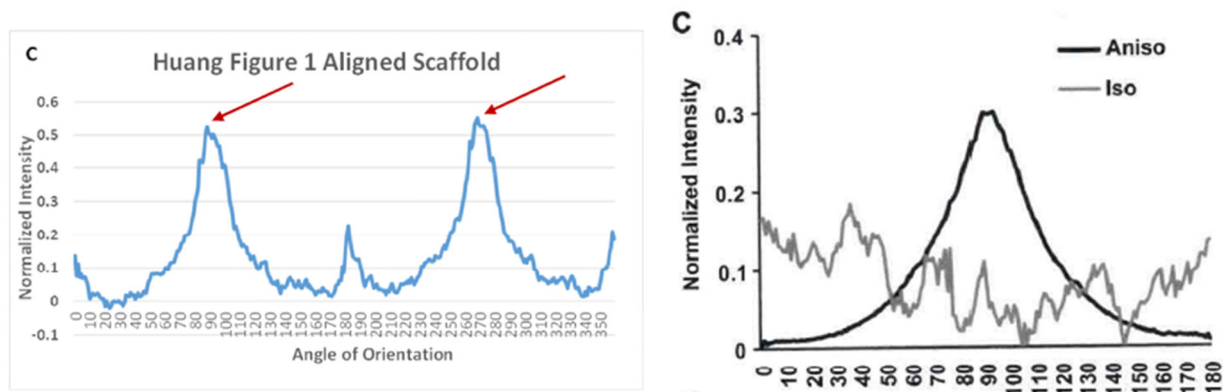
As shown below with Petitioner’s annotation, Huang2 discloses a *single* peak.



Pet. 36; Ex. 1005, 1794 (“[t]he narrow peak”). Because only one peak is disclosed, that sole peak controls the average height of the peaks in the result. In other words, the height of the sole peak *is identical to*—not higher than—the average height of the peaks in the result. The height of both the sole peak and the average are the same: 0.3 Normalized Intensity units. Ex. 2015 ¶ 76. Accordingly, Huang2’s single peak is not a “major ... peak” as claimed because its height is not higher than the average height of the peaks in the result. *Id.* ¶ 77.

Petitioner also relies upon a FFT plot created by Dr. Simpson’s post-hoc testing of a reproduced image of Huang2’s fibers. Pet. 38. As discussed below and incorporated herein, this testing deviated from the FFT protocol applied by Huang2; it should not be considered. *Infra* § V.B.3.a; Ex. 2015 ¶ 78 (“[A] POSITA would not credit the post-hoc testing performed by Dr. Simpson over the authors’ own published FFT analysis result.”).

Moreover, Dr. Simpson’s testing produced a FFT result that directly conflicts with Huang2. As shown below, Dr. Simpson’s testing depicts two minor peaks in the FFT plot, at 0° and 180°, that are *absent* and not disclosed by Huang2.



Compare Ex. 1003 ¶ 125, with Ex. 1005, Fig. 1C; Ex. 2015 ¶ 79.

Dr. Simpson’s post-hoc FFT plot is “plainly inconsistent” and “flatly contradicted” by Huang2, which expressly discloses a FFT plot without any additional peaks. Dr. Simpson’s inconsistent result should not be considered. *Homeland Housewares, LLC v. Whirlpool Corp.*, 865 F.3d 1372, 1378 (Fed. Cir. 2017) (“[W]e must disregard the testimony of an expert that is plainly inconsistent

with the record.”); *Honeywell Int’l Inc. v. 3G Licensing, S.A.*, 124 F.4th 1345, 1354 n.6 (Fed. Cir. 2025) (“[O]n its face, this statement conflicts with the plain language of the Philips reference [W]e are not required to uncritically accept expert testimony that is flatly contradicted by the record.”). As Dr. Mikos testifies, “a POSITA would credit the Huang2 reference itself and would not credit Dr. Simpson’s post-hoc testing, which conflicts with Huang2’s disclosure, in part because Huang2 performed more reliable FFT analysis than Dr. Simpson did,” as Dr. Mikos explains further in his declaration. Ex. 2015 ¶ 80; *infra* § V.B.3.

Petitioner chose to rely upon Huang2, and Petitioner bears the burden of proving that Huang2 discloses the claimed “major adjacent peaks” by a preponderance of evidence. It cannot meet that burden by, on the one hand, relying on Huang2 for *some* limitations of the claim while, on the other, asking the Board to ignore Huang2’s disclosure and instead rely upon contradictory extrinsic evidence to suggest other limitations absent any rationale to do so.

This is especially salient in *inter partes* review (“IPR”), which must be based on “patents or printed publications.” 35 U.S.C. § 311. Review may not be based on expert testimony that contradicts a reference’s clear disclosure. PTAB Consolidated Trial Practice Guide (“CTPG”) (Nov. 2019) at 36 (“[B]ecause [IPR] may only be requested ‘on the basis of prior art consisting of patents or printed publications’ ...

expert testimony cannot take the place of disclosure from patents or printed publications.”).

Here, the printed publication upon which Petitioner relies depicts a FFT result without *any* additional peaks and, accordingly, lacks the claimed “major adjacent peaks” as properly construed. Ex. 2015 ¶¶ 73-81.

3. Huang2 lacks “major adjacent peaks that are about 180° apart from each other”

a) Dr. Simpson’s post-hoc FFT analysis is entitled to no weight

Dr. Simpson states that he “conducted [his] own analysis of Figure 1B using the FFT analysis and ImageJ software described in Huang2 and the ’227 patent.” Ex. 1003 ¶ 125. This is incorrect. Dr. Simpson’s testing is plainly inconsistent with Huang2 and, therefore, cannot credibly interpret Huang2’s disclosure. *Homeland Housewares*, 865 F.3d at 1378 (“[W]e must disregard the testimony of an expert that is plainly inconsistent with the record.”).

(1) The tested image is different (and insufficient)

Dr. Mikos testifies that “[i]mage quality is the single most important factor in FFT testing.” Ex. 2015 ¶ 87 (“Poor image quality that lacks sufficient contrast, resolution, and/or brightness results in invalid and inaccurate test results.”); Ex. 2017, 58:25-59:18 (Dr. Simpson explaining that image acquisition is the most important step in FFT analysis), 142:14-15 (“You should always be collecting data with the best capability that you have.”); Ex. 1003 ¶ 179 (Dr. Simpson discarding

one image to instead rely upon “higher quality images”). Without a sufficient image, FFT testing results cannot be credited. Ex. 2015 ¶¶ 87-89.

Here, however, Dr. Simpson did not test high quality images. Ex. 2015 ¶ 86. Instead, Dr. Simpson performed FFT analysis on an Adobe PDF reproduction of Huang2’s SEM image. Ex. 2017, 138:23-139:16 (Dr. Simpson stating that he tested a downloaded PDF image), 157:8-14 (stating that this is “not something I do routinely”).⁶ Performing FFT analysis on a reproduction of a SEM image can lead to invalid and inaccurate results. Ex. 2015 ¶ 88.

Reproduced images like that used by Dr. Simpson introduce noise, blur, and uneven illumination to the analysis. *Id.* Image contrast is reduced and fine details—essential to a reliable FFT result—are lost. *Id.* (“A POSITA would not find a reproduced or photocopied image to be suitable for FFT analysis.”); Ex. 1010, 609 (Dr. Simpson acknowledging that uneven illumination introduces error), 612 (acknowledging that noise introduces artifacts into the result). Dr. Mikos testifies that noise and artifacts introduced by testing reproduced images adversely affect FFT plot shape with high frequency features, reflecting fiber orientation, most

⁶ Dr. Simpson did not document or account for any image compression performed on the image when converting it to PDF form. *Id.*

affected. Ex. 2015 ¶ 88.

Both Dr. Mikos and Dr. Simpson testified they do not normally perform FFT analysis with reproduced or photocopied images. Ex. 2015 ¶ 88; Ex. 2017, 157:8-14, 157:23-158:3 (Dr. Simpson testifying that he does not advise his students to test reproductions).

(2) Huang2's image was tested differently

Huang2 obtained SEM “images of *five* randomly selected areas” of the scaffold. Ex. 1005, 1792 (emphasis added). “Representative SEM images of the electrospun fibers were cropped into a square covering as much of the image as possible.” *Id.* Huang2 then performed FFT analysis “on the SEM images of [the] randomly selected areas ($n = 5$).” *Id.* at 1794. But this is not what Dr. Simpson did. Instead, Dr. Simpson “cropped and masked” a photocopy of a *single* SEM image (i.e., a reproduction of Huang2's Figure 1B) and used that single *masked* image for FFT analysis. Ex. 1003 ¶ 125 (figures and caption); Ex. 2017, 137:2-5.

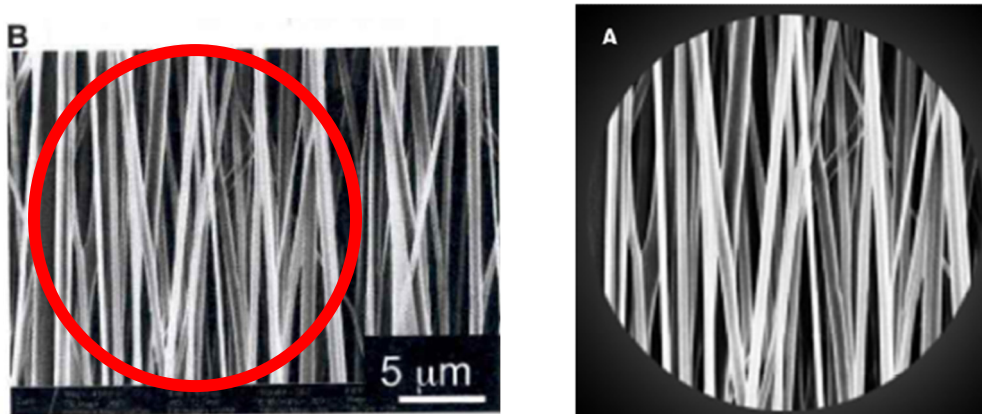
First, Dr. Simpson “misinterpreted” Huang2's disclosure and incorrectly “believe[d] that [Huang2] used a mask.” Ex. 2017, 144:11-13. Given that error, Dr. Simpson inappropriately used a mask in his FFT analysis. *Id.* at 146:11-12 (“I used a circular mask because I misread that sentence.”). There is now no dispute, however, that Huang2 did not use a mask. Ex. 2015 ¶ 90; Ex. 1005, 1792 (describing

FFT without a mask; citing “[22],” i.e., Ex. 1013, which also lacks a mask).⁷

Inclusion of a mask *directly* impacts the resulting FFT plot. As reported in Dr. Simpson’s 2008 paper, for example, FFT analysis of an unmasked image with 45°-oriented fibers produces a FFT plot that depicts “edge noise” as “small peaks on either side of the alignment peaks.” Ex. 1010, 615. However, “[p]rocessing the image with a window mask removes this spurious information.” *Id.* In other words, inclusion or exclusion of a mask is not a trivial detail; it dictates that “different peaks [will be] included or excluded” from the resulting FFT plot. Ex. 2015 ¶ 94.

Second, although Huang2 performed FFT on *five* SEM images, Dr. Simpson tested only one (and a photocopy at that). Even worse, Dr. Simpson’s improper use of a mask discarded a large portion of the *single* image that he tested, as shown below.

⁷ Dr. Simpson argues that a mask is consistent with his 2008 paper (Ex. 1010). Ex. 2017, 163:16-164:5. But that is not incorporated in Huang2. Moreover, the 2008 paper discloses an *optional* mask—an option not exercised in the ’227 patent. Ex. 1001, Fig. 8A (depicting the tested image without a mask).



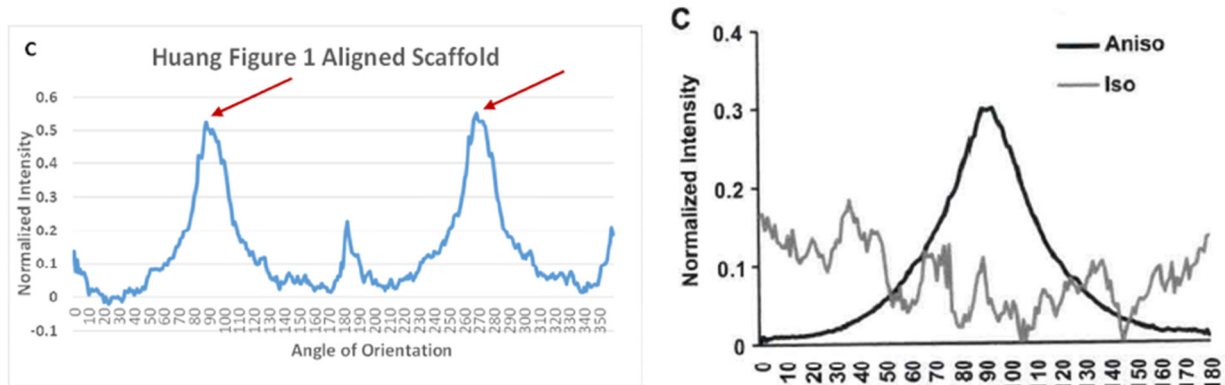
Ex. 1005, 1793 (left, annotated with a red circle to approximate the mask applied by Dr. Simpson); Ex. 1003 ¶ 125 (right, the single masked image that Dr. Simpson tested); Ex. 2015 ¶¶ 92-93.

Dr. Simpson’s approach violates his past practice. Previously Dr. Simpson admonished: “measurements of scaffold anisotropy should be averaged over as large as an area as possible” because “[l]ocal variations in fiber alignment *can bias the 2D FFT process.*” Ex. 1010, 606 (emphasis added). To avoid bias, Dr. Simpson previously recommended that “alignment data can be *captured from several sites in a scaffold and averaged* to circumvent the limitations inherent when a small sample surface area must be used.” *Id.* (emphasis added). Dr. Simpson took no such efforts here. Ex. 2015 ¶ 93 (“A POSITA would recognize that Dr. Simpson’s testing would produce inaccurate results because he utilized such a small portion in his testing.”).

In short, Dr. Simpson did *not* perform the FFT analysis described in Huang2. Dr. Simpson’s approach to testing her also violated his own past practices.

(3) The FFT result is different

As referenced above, *supra* § V.B.2, Dr. Simpson's FFT result *is not the same* as Huang2's. It varies in three manifest respects, casting doubt on its validity. Dr. Simpson's FFT plot and Huang2's are reproduced below.



Compare Ex. 1003 ¶ 125, with Ex. 1005, 1793.

Dr. Simpson's testing produced a markedly different result than Huang2. Ex. 2015 ¶¶ 96-97. First, while Huang2's FFT plot depicts a broad curve extending from 0° to 180°, Dr. Simpson's plot depicts a much narrower curve, extending at most from 20° to 140°. *Id.* ¶ 98. Second, while Huang2's peak reaches a maximum height of 0.3 normalized intensity units, Simpson's peaks extends 83% higher, to 0.55 normalized intensity units. *Id.* ¶ 99. Third, as detailed above, *supra* § V.B.2, while Huang2's FFT lacks any minor peaks, Simpson's FFT depicts two, at 0° and 180°. *Id.* ¶ 100. These FFT analyses convey fundamentally *different* results and, accordingly, convey fundamentally *different* information about the underlying fibers. *Id.* ¶ 101.

As discussed above, the height and overall shape of the most prominent peaks convey the degree of fiber alignment, where “[a] high and narrow peak indicates a more uniform degree of fiber alignment, [but] a broad peak, or a shoulder on the peak indicates that more than one axis of alignment may be present.” Ex. 1010, 610. Dr. Simpson made clear during his deposition that these are relative terms; a peak is “narrow” or “broad” only in relation to other peaks. Ex. 2017, 99:2-7 (explaining that “high and narrow” is “a relative description between those two samples”), 100:13-14 (“It’s only broad relative to a peak that is -- that it could be compared to.”). To that end, Dr. Simpson normalized his FFT plot precisely so that it could be compared against Huang2’s. *Id.* at 166:1-11 (explaining that he normalized his data because “I was comparing Huang to Huang.”). But, despite having normalized his data, Dr. Simpson fails to reconcile the differences that appear in his FFT plot as compared to Huang2’s. Ex. 2015 ¶¶ 96-101.

In reviewing Dr. Simpson’s FFT plot as compared to Huang2, even when normalized, they clearly present inconsistent findings. *Compare* Ex. 1003 ¶ 110, *with* Ex. 1005, 1793. Specifically, the relatively “high and narrow peak” depicted in Dr. Simpson’s testing shows “a more uniform degree of fiber alignment” (Ex. 1010, 601) than reported by Huang2. Ex. 2015 ¶ 98. By contrast, Huang2’s relatively shorter and broader peak conveys “that more than one axis of alignment may be present” (Ex. 1010, 610). *Id.* Petitioner fails to address these differences.

Id. (“Given that both sets of FFT results purport to reflect the same set of fibers, this discrepancy alone renders Dr. Simpson’s results unreliable.”).

In terms of FFT peak height, Dr. Simpson’s testing again presents inconsistent findings. Ex. 2015 ¶ 99 (comparing 0.3 versus 0.55 normalized intensity units). Dr. Simpson published that “the onset of anisotropic properties in an electrospun scaffold ... [appear] at a threshold alignment value of 0.05 units.... Once alignment values of 0.05 units are detected [in] this type of scaffold, stress at failure will increase incrementally as a function of approximately 0.01 2D FFT alignment units.” Ex. 1010, 610. Accordingly, a POSITA would understand that anisotropic properties like stress at failure for Huang2’s fibers would be notably *higher* based on Dr. Simpson’s testing (0.55 normalized units) than for Huang2’s results (0.3 normalized units), which again renders Dr. Simpson’s testing unreliable. Ex. 2015 ¶ 99.

Finally, as discussed above, the presence of minor peaks in Dr. Simpson’s FFT result, which are affirmatively absent from Huang2’s FFT result, presents yet another inconsistency in Dr. Simpson’s FFT plot. Given that both sets of FFT results purport to reflect the same set of fibers from the same image, this discrepancy alone renders Dr. Simpson’s results unreliable. Ex. 2015 ¶ 100.

Given these differences, a POSITA would recognize that Dr. Simpson’s FFT testing purports to convey fundamentally *different* information about the underlying

fibers than Huang2 discloses. A POSITA would disregard Dr. Simpson's testing. Ex. 2015 ¶ 101.

(4) Conclusion

Dr. Simpson's testing conflicts with the printed publication upon which Petitioner nominally relies. It warrants no weight in this IPR, which must be based upon patents or printed publications. *Homeland Housewares*, 865 F.3d at 1378 (“[W]e must disregard the testimony of an expert that is plainly inconsistent with the record.”); CTPG at 36 (35 U.S.C. § 311(b) dictates that “expert testimony cannot take the place of disclosure from patents or printed publications”).

b) The FFT protocol is insufficiently explained

With this background of conflict, Dr. Simpson's statement that he “conducted [his] own analysis of Figure 1B using the FFT analysis ... described in Huang2 and the '227 patent” is insufficient to satisfy 37 C.F.R. § 42.65(b). *Luitpold Pharms., Inc. v. Kovi*, IPR2018-01640, Paper 19 at 23-24 (PTAB Mar. 6, 2019) (finding insufficient an expert declaration that “fails to provide any specificity as to the steps taken”).

Dr. Simpson testified that a POSITA typically documents the steps taken in performing FFT analysis, and that Dr. Simpson *required* that his students do so. Ex. 2017, 59:19-60:8 (“[Y]ou would certainly document the parameters that you're using so you can reproduce them over and over and over and over and over again.”),

60:19-23; Ex. 2015 ¶ 102 (“[I]t is customary for a POSITA to document all aspects of their testing such that others may evaluate the test results in view of the protocol employed and, if desired, reproduce those results.”).

Dr. Simpson’s declaration, however, does not even identify the *version of software* he used to conduct his analysis, let alone the parameters he applied. Ex. 2017, 140:24-141:4. Likewise, Dr. Simpson did not document where or how he applied the circular projection in the ImageJ software to generate his FFT plot, a “critical” aspect of FFT analysis. *Id.* at 150:10-18; Ex. 2015 ¶ 104 (“[I]f the circular selection does not capture a representative portion of the FFT output image, it will bias the results.”). In this vacuum, reproducing Dr. Simpson’s testing is impossible. Ex. 2015 ¶ 104. Petitioner cannot meet its burden by relying upon testing undertaken with a non-reproducible protocol.

Dr. Simpson’s earlier paper, incorporated by reference into the ’227 patent, describes other critical aspects of FFT analysis that are essential to accurate testing, that were not accounted for in Dr. Simpson’s testing, and which *directly impact* the validity of FFT testing and the shape of the resultant FFT plot. Ex. 2015 ¶ 105. For example, Dr. Simpson’s earlier paper emphasizes the importance of image quality to reliable FFT testing. In the 2008 paper, Dr. Simpson utilized images that were “stored and analyzed as uncompressed .TIF files to preserve image integrity [precisely because] the image compression used in .JPG format will degrade image

integrity.” Ex. 1010, 607. In his post-hoc testing, however, Dr. Simpson “ha[d] no idea” how Huang2’s image was stored and did not attempt to account for that in his analysis. Ex. 2017, 140:17-19; Ex. 2015 ¶ 105. Likewise, in 2008, Dr. Simpson identified risks associated with uneven illumination of an image: “Care should be taken at the time of image capture to optimize sample illumination; uneven illumination can complicate and introduce error into the alignment analysis.” Ex. 1010, 609. Again, here, Dr. Simpson “ha[d] no idea” if sample illumination was optimized for Huang2’s image and did not attempt to improve the image’s illumination. Ex. 2017, 135:14-19; Ex. 2015 ¶ 106. Likewise, despite previously recognizing the impact of optical and electronic noise on FFT analysis, Dr. Simpson did not account for the presence of such noise in his reproduction of Huang2’s figure. Ex. 1010, 609; Ex. 2015 ¶ 107.

As discussed by Dr. Mikos, testing a reproduced image detracts from the image quality that is essential to FFT testing and introduces noise, blur, and/or uneven illumination, all of which adversely affect the resulting FFT plot shape. Ex. 2015 ¶¶ 103, 108-109. High frequency features of the FFT plot, which reflect alignment, are most affected. *Id.* ¶ 109.

It was Petitioner’s burden to demonstrate anticipation; that burden cannot be satisfied with incomplete, undisclosed, and non-reproducible post-hoc testing that violates 37 C.F.R. § 42.65(b). Dr. Simpson’s results cannot be credited. Ex. 2015

¶¶ 102-114 (also discussing the impact of normalization and a mask, as discussed above). For these reasons, Huang2 does not anticipate independent claim 1.

4. Huang2 and Kuo do not render obvious the “repair [of] a tendon, a ligament or a nerve defect”

Claim 1 requires “applying the scaffold to the tissue defect to repair a tendon, a ligament or a nerve defect.” Ex. 1001, 23:36-37. Petitioner alleges that a POSITA would have used Huang2’s scaffold to do so based upon Kuo because they are allegedly in “the same field of art, and both seek to solve the same problems” related to the creation of aligned scaffolds that mimic native tissue. Pet. 29-30, 39-41.

a) Common fields or problems are not sufficient

Even if Huang2 and Kuo are in the same field and/or solve the same problem, that is not a sufficient rationale to modify Huang2. Pet. 29-30; *Sisvel Int’l S.A. v. Sierra Wireless, Inc.*, 82 F.4th 1355, 1364 (Fed. Cir. 2023) (“[A]ssertions that the references were analogous art ... is an insufficient articulation for motivation to combine.”); *Securus Techs., Inc. v. Global Tel*Link Corp.*, 701 Fed. App’x 971, 977 (Fed. Cir. 2017) (unpublished) (“[F]alling within the same alleged field ... is not enough for [Petitioner] to meet its burden of presenting a sufficient rationale.”).

b) Huang2 is incapable of repairing tendon, ligament, or nerve

Huang2 and Kuo are not interchangeable merely because both teach aligned fibers. Pet. 29-30, 39-41.⁸ Dispositive differences counsel against the combination. Ex. 2015 ¶¶ 116-117 (“[R]epairing tendon, ligament, or nerve tissue requires *more* than an aligned scaffold.”).

(1) Kuo requires a jelly-roll configuration

Kuo discloses several essential steps to repair the claimed tissues. Pet. 39. First, Kuo seeds the appropriate cell type on the scaffold; second, Kuo rolls the scaffold in a “jelly-roll like manner”; third, Kuo implants the “spirally wound tissue construct” in a subject to replace muscle, nerve, ligament, or tendon tissue. *Id.* (quoting Ex. 1018 ¶¶ 22-23). This rolled structure “mimic[s] the native microstructure of tendon/ligament ... and avoids poor cell seeding ... [which] is a major limitation of aligned scaffolds.” Ex. 1018 ¶¶ 112.

As just described, Kuo’s treatment of these tissues turns on its unique “jelly-roll” structure. But Huang2 does not disclose a rolled scaffold, nor does Petitioner

⁸ Petitioner’s hindsight is evidenced by its characterization of “tendon or ligament” as “the target tissue.” Pet. 30. It is improper to use the claim itself as a “target” or roadmap. *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996).

propose modifying Huang2 to present such a structure. Pet. 39-41. Accordingly, a POSITA would not have utilized Huang2 to treat the claimed tissues absent the rolled structure that is essential to Kuo's treatment. Ex. 2015 ¶¶ 118-121; DI 33 (It is "not clear why ... a POSITA would have chosen to use Huang2's scaffold in place of the scaffolds taught by Kuo for the repair of tendon, nerve, or ligament tissue when Huang2 does not teach the same rolled structure that mimics the natural tendon, nerve, or ligament tissue.").

In fact, Dr. Mikos explains that Huang2's two-dimensional scaffold mimics skin, Ex. 2015 ¶ 120, while Kuo's rolled, three-dimensional structure mimics tendon/ligament/nerve fascicles. *Id.* ¶ 118 (explaining that Kuo avoids what it perceives as "defects in two-dimensional scaffolds like Huang2's (i.e., poor cell seeding)"). These different scaffold structures are necessary to repair the different tissue structures. *Id.* ¶¶ 119 (explaining that Kuo's "rolled structure *does not* mimic two-dimensional skin tissue, for which Huang2's scaffold is designed" and Huang2's scaffold "does not mimic three-dimensional tendon, ligament, or nerve fascicles, for which Kuo's scaffold is designed"). In other words, a POSITA would not have expected success in using Huang2's scaffold to repair tendon, ligament, or nerve tissue absent the unique rolled, three-dimensional shape that mimics fascicle structure. *Id.* ¶ 120

Even if Petitioner had proposed to do so (it did not), a POSITA would not have rolled Huang2's scaffold because doing so presents known drawbacks. For example, Dr. Mikos explains that rolled structures may lead to cell death internal to the scaffold due to insufficient perfusion. Ex. 2015 ¶ 122 (explaining that two-dimensional scaffolds like Huang2's possess superior exposure to essential nutrients and oxygen as compared to rolled scaffolds); Ex. 2023, 145 (“[T]he seeded cells may experience malnutrition or decreased concentrations of growth factors vital for their growth and differentiation.”).

Dr. Simpson himself identifies numerous problems associated with rolled scaffolds. Ex. 2022. For example, rolled scaffolds present “‘seams’ where the edges of the rolled sheets are surface exposed ... resulting in discontinuities and possible weak connective points in the structure.” *Id.* at 3:54-63. When used for nerve repair, these characteristics cause axons to “cluster and grow as a jumbled disorganized mass,” which is “associated with reduced axon targeting.” *Id.* at 5:39-46. Even when “rolled tightly into more compact structures,” problems persist including “large seams” that risk “infiltration by unwanted interstitial fibroblasts and or inflammatory cells.” *Id.* at 3:63-4:8, 31:66-32:3; Ex. 2015 ¶ 123.

Simply put, the Petition does not explain *why* a POSITA would have attempted to use Huang2's two-dimensional scaffold to repair tendons, ligaments, or nerves without the rolled structure disclosed by Kuo or, on the other hand, *why* a

POSITA would have instead rolled Huang2's scaffold to facilitate such repair in the face of known disadvantages of rolled scaffolds. Ex. 2015 ¶ 124. This combination is premised entirely on hindsight.

Petitioner's allegation that Huang2 and Kuo both use aligned fibers for tissue repair does not demonstrate obviousness. Pet. 39-41. Kuo relies primarily upon its rolled structure to repair tendon, ligament, and nerve; aligned fibers are utilized in *some* embodiments as an optional feature. In fact, Kuo explains that its fibers may be "random, aligned, or any combination thereof." *E.g.*, Ex. 1018 ¶ 5; Ex. 2015 ¶ 121.

(2) Huang2's elastic modulus is insufficient

The elastic modulus of a scaffold—a measurement of stiffness—is the most important mechanical property for tissue repair. Ex. 2015 ¶ 125. To be effective, it must match the elastic modulus of native tissue so seeded cells will differentiate and develop appropriately. *Id.* ¶¶ 127-128 Ex. 2024, Abstract ("Naive mesenchymal stem cells (MSCs) are shown here to specify lineage and commit to phenotypes with extreme sensitivity to tissue-level elasticity. Soft matrices that mimic brain are neurogenic, stiffer matrices that mimic muscle are myogenic, and comparatively rigid matrices that mimic collagenous bone prove osteogenic."); Ex. 2017, 172:16-21.

The elastic modulus of tendon, ligament, and nerve vary markedly from that

of skin tissue and Huang2's skin scaffold. Specifically, Huang2's aligned skin scaffold presents an elastic modulus of 8.98 MPa (Ex. 1005, 1794), while the elastic modulus of tendon and ligament tissue is up to 660 and 447 MPa, respectively. Ex. 2015 ¶ 129 (summarizing values; citing Ex. 2026, 801; Ex. 2027, 649; Ex. 2028, 429; Ex. 2029, 511). A POSITA would not have utilized Huang2's skin scaffold to repair tissues that require up to 73 and 49 times *more stiffness* to function properly (tendon and ligament, respectively). Ex. 2015 ¶¶ 131, 133. Huang2's scaffold would be too compliant to handle the large loads borne by these tissues. *Id.* ¶ 131 ("Huang2's scaffold would be entirely insufficient to perform the functions required by tendon and ligament, which are very stiff load-bearing tissues.").

Likewise, nerve requires 472 times *less* stiffness than that of Huang2's scaffold. *Id.* ¶¶ 129 (0.012-0.019 MPa), 132-133; Ex. 2030, 2722. Accordingly, Huang2's scaffold would be unsuitable to repair nerve tissue, having too much stiffness to function properly. Ex. 2015 ¶ 132 ("Huang2's skin scaffold would impart too much stiffness, which would hinder effective nerve repair.").

A POSITA would not have used Huang2 as proposed, given these differences in the mechanical properties of Huang2's scaffold, as compared to the target tissue to be repaired, which preclude effective repair. Ex. 2015 ¶¶ 125-133.

(3) Huang2's structure and seeded cell types are insufficient

Huang2's scaffold is designed only for skin tissue repair and is seeded with

normal human dermal fibroblasts (“NHDF”) to achieve that function. Ex. 1005, 1792. NHDF are cells unique to skin. Ex. 2015 ¶ 135 (“NHDF are cells isolated from the human dermis.... NHDFs are *not* typically used to repair tendon, ligament, or nerve tissue because other types of cells are more particularly targeted to those tissue types.”).

Kuo discloses scaffolds seeded with different cell types for repair of the appropriate tissue type. Ex. 1018 ¶ 58 (“[D]ifferent cell types or combinations thereof may be employed ... depending upon the intended function of the tissue engineered construct being produced.”). In other words, the specific cells seeded on Kuo’s scaffold facilitate growth of that specific tissue type. *Id.* ¶¶ 16 (disclosing various cell types), 67 (disclosing various tissue types); Ex. 2015 ¶ 136 (“Every type of specifically differentiated cell type is associated with the growth or repair of an associated tissue type.”).

Other mechanical properties of the scaffold must also be calibrated to the specific tissue to be repaired, including stiffness and degradation rate, to ensure appropriate cell growth. Ex. 2015 ¶ 138 (“The mechanical properties of the scaffold substrate must be calibrated to the tissue type that will be repaired in terms of, among others, scaffold stiffness (as discussed above regarding elastic modulus) and scaffold degradation rate.”), *id.* ¶ 139 (“[T]he rate at which the scaffold degrades must be controlled to match the rate of new tissue formation.”); *supra* § V.B.4.b.2

(discussing differences in stiffness); Ex. 2024, Abstract.

Petitioner fails to account for any of these structural differences. Indeed, the cell type seeded on each scaffold dictates the type of tissue that may be repaired with that scaffold. Ex. 2015 ¶ 136. Huang2’s scaffold is seeded with NHDF to support skin tissue repair; a POSITA 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.* ¶ 137 (“NHDF cells do not generate tendon, ligament, or nerve tissue—they generate skin tissue.”).

Moreover, to facilitate growth of the claimed tissue types, “a POSITA would have expected Huang2’s and Kuo’s scaffolds to employ different ratios of polymers to appropriately control the rate of degradation to match the appropriate rate of ECM secretion for each different tissue type.” Ex. 2015 ¶ 140. To that end, Dr. Mikos explains that “a POSITA would have understood that the tissue regeneration rate of skin is much faster than that of muscle, nerve, ligament, or tendon because of the abundance of stem cells and the richness of blood supply that is present in skin as compared to muscle, nerve, ligament or tendon.” *Id.*

But none of this is accounted for in the Petition. The Petition does not explain how, e.g., tendon tissue would have been repaired with Huang2’s NHDF-seeded scaffold. Pet. 30. Indeed, Kuo itself demonstrates that when tendon repair is intended, the scaffold is seeded with *tendon* cells (tenocytes) or stem/progenitor cells

that differentiate into tendon tissue. Ex. 1018 ¶¶ 16, 112; Ex. 2003, 3; Ex. 2004, 3; Ex. 2015 ¶ 141. Nor does Petitioner propose modifying Huang2 to incorporate alternate cell types or structural scaffold conditions to support alternate types of tissue repair. Pet. 28-30, 39-41.

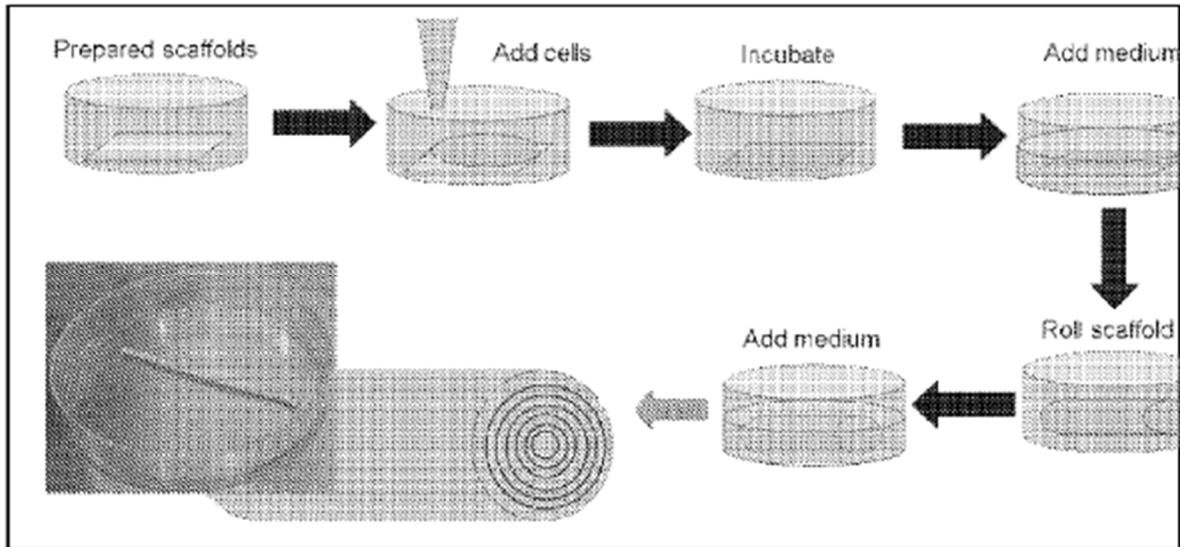
5. Dependent claims 2-6 would not have been obvious

Dependent claims 2-6 include all limitations of independent claim 1 and, accordingly, Petitioner's contentions likewise fail.

a) Claim 2

Dependent claim 2 further recites that "the scaffold is in the form of one or more elongated sheets." Ex. 1001, 23:38-39. Petitioner relies upon Huang2 and Kuo as disclosing a scaffold sheet. Pet. 41.

As described above, Kuo teaches a scaffold that is "spirally wound in a jelly-roll like manner." Ex. 1018 ¶¶ 5, 7, 112. Plainly, a spirally rolled structure, shown below, is not a "sheet." Ex. 2015 ¶ 146.



Ex. 1018, Fig. 1.

Petitioner’s reliance upon Kuo to teach tendon, ligament, or nerve repair requires a rolled structure that is not a “sheet,” as a POSITA would understand that term. Ex. 2015 ¶ 145 (defining a “sheet” as “something that is substantially thinner in one dimension than in all other dimensions”); Ex. 2032, S22; Ex. 2033, 1632; Ex. 2017, 194:5-8 (Dr. Simpson testifying that a “sheet” is an “[e]xtended flat surface ... It’s not a cube, it’s not a circle”).

Petitioner’s contention that a POSITA would have been motivated to use a sheet is nonsensical in this combination, given Kuo’s necessary use of a rolled scaffold. Pet. 41; Ex. 1003 ¶¶ 137-142. Without support, Petitioner concludes that a POSITA “would have been motivated ... to use Huang2’s aligned fibers in scaffolds in the form of one or more elongated sheets as disclosed by Kuo.” Pet. 41. But the cited portions of the Petition and declaration are utterly silent as to *any*

reason why a POSITA would have done so. *Id.* (citing Pet. § X.A and Ex. 1003 § VI.A.2, both of which fail to discuss motivation to use a sheet); Ex. 1003 § VI.A.2 (citing Ex. 1003 § VI.A.1, which itself fails to discuss motivation to use a sheet). Simply put, there is no such motivation to use a sheet, where Kuo’s repair turns on the presence of a rolled scaffold that mimics tendon, ligament, or nerve.

b) Claim 3

Dependent claim 3 further recites that “the scaffold is a composite of multiple layers of one or more sheets.” Ex. 1001, 23:40-41. Petitioner alleges that Kuo teaches “multiple ‘sheets’ in the scaffold.” Pet. 41-43. Petitioner also alleges that multi-layered sheets were well known and that a POSITA “would have been motivated ... to use Huang2’s aligned fibers in scaffolds in the form of multiple layers of one or more sheets as disclosed by Kuo.” *Id.*

Petitioner misapprehends Kuo’s disclosure, which does not disclose multiple sheets; instead, Kuo simply uses the plural form of the term “sheet” when describing the “shapes” or composition of its scaffold. Pet. 41-42; Ex. 1018 ¶¶ 24 (explaining that scaffold “shapes or forms include, ... films ... ribbons, cords, sheets, flat discs, cylinders, spheres, 3-dimensional amorphous shapes”), 34; *contra, e.g., id.* ¶ 7 (disclosing a singular “porous scaffold sheet ... wherein the sheet is spirally wound”).

Moreover, even if “multi-layer sheets” were “used extensively in the scientific

literature,” Pet. 42, the Petition does not explain *how or why* a multi-layer sheet would have been employed in the combination of Huang2 and Kuo. Ex. 2015 ¶ 150 (explaining that rolling multiple layers would exacerbate difficulties associated with rolled scaffolds). The arguments made above regarding claim 2 are incorporated herein. The Petition simply concludes that a POSITA “would have been motivated” to do so, without answering the most important questions: “why?” and “how, while still repairing the claimed tissue types.” As with claim 2, Petitioner provides no such reasoning. Pet. 42-43.

c) Claims 4, 5, and 6

Dependent claims 4, 5, and 6 further specify that “the tissue defect is” a nerve defect, ligament defect, or tendon defect, respectively. Ex. 1001, 23:42-24:4. As discussed above, the combination of Huang2 and Kuo does not render obvious the treatment of these specific tissue defects.

C. Ground 2: Neither Lee alone nor in combination with Kuo render claims 1-6 obvious

1. The Petition does not satisfy 35 U.S.C. § 312(a)(3)

Claim 1 recites a FFT analysis that “demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other.” Ex. 1001, 23:32-35. Petitioner contends that “Lee by itself also discloses this element,” or “at the very least, this element would have been obvious in view of Lee alone.” Pet. 47, 51.

The theory upon which Petitioner relies is unclear. Petitioner does not identify with particularity *any* basis for finding that Lee “discloses this element,” whether expressly or inherently. 35 U.S.C. § 312(a)(3). Nor does Petitioner identify with particularity *any* basis for finding that this would have been obvious over Lee. Rather, Petitioner’s obviousness contentions turn on whether the prior art taught or motivated a POSITA to conduct an FFT analysis of Lee’s fibers, Pet. 50-51, which presents a question that the Board found to be beside the point in a related proceeding. IPR2025-00248, Paper 14 at 38 (PTAB Aug. 5, 2025).

It is Petitioner’s burden to plead “with particularity” and Petitioner falls short here. *Med-El Elektromedizinische Gerate GES.M.B.H v. Sonova AG*, IPR2021-00023, Paper 28 at 21 (PTAB Mar. 2022) (“The purpose of § 312(a) is to ensure Patent Owner is on notice of the allegations forming the basis of the challenges against the subject patent.”); *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (“[T]he petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.”).

2. Lee lacks “major adjacent peaks that are about 180° apart from each other”

a) Lee does not expressly disclose this limitation

First, regarding express anticipation, the Petition does not assert that Lee discloses FFT *at all*, much less the claimed FFT analysis result. Pet. 47-51; Ex. 1011. Lee cannot expressly disclose the claimed FFT analysis result when FFT

is not employed. Ex. 2017, 154:8-10 (“Q. Does Lee disclose using FFT to measure alignment? A. No.”); Ex. 2015 ¶ 154.

b) Lee does not inherently disclose this limitation

Second, regarding inherent anticipation, the Petition does not discuss “inherency,” “inherent” properties, or “necessarily present” characteristics at all when discussing Lee. Pet. 47-51; Ex. 2015 ¶ 156. As noted in the Decision on Institution, “Petitioner does not clearly assert in the Petition that the fibers taught by Lee necessarily or inherently satisfy the claimed FFT analysis result.” DI 36 (“Petitioner’s grounds based on Lee may ultimately fail on the merits due to this lack of specificity.”).

Instead, Petitioner contends that a POSITA “would know that the degree of alignment could also be determined using ImageJ software to run an ‘FFT analysis,’” which would confirm fiber alignment. Pet. 50. But Petitioner’s contentions regarding what a POSITA could do are insufficient to invoke inherency let alone to establish by a preponderance of the evidence that the limitation is inherently (necessarily, inevitably) present. The Petition makes no such allegation.

Petitioner fails to show that major adjacent peaks are necessarily present in Lee’s fibers simply because a POSITA *could* run FFT, which Petitioner alleges would show the fibers oriented in an aligned manner. Pet. 50-51. A contention that FFT would show fibers “oriented ... in an aligned manner” is not a contention that

Lee's fibers necessarily include the claimed FFT result with "major adjacent peaks that are about 180° apart from each other." Pet. 50; Ex. 2015 ¶ 156. Moreover, that Dr. Simpson purports to have run a single FFT analysis is not a contention that the fibers taught by Lee necessarily or inherently satisfy the claimed FFT analysis result. Pet. 50-51.

Inherency demands more. "The keystone of the inherency doctrine is inevitability.... Absent inevitability, inherency does not follow even from a very high likelihood that a prior art method will result in the claimed invention." *In re Montgomery*, 677 F.3d 1375, 1384 (Fed. Cir. 2012) (Lourie, A., dissenting).

Any showing of inherency must have been presented in the Petition. Pet. 47-51 (citing Ex. 1003 ¶¶ 175-187). It cannot be incorporated by reference to Dr. Simpson's declaration. However, even if it *could* be incorporated by reference, the Petition fails to cite any portions of Dr. Simpson's declaration to support an inherency theory regarding Lee. Indeed, the cited portions *also* fail to mention inherency or necessarily present characteristics. Ex. 1003 ¶¶ 175-187.

c) Lee does not render obvious this limitation

Third, regarding obviousness, Petitioner alternatively contends that a POSITA "would know that the degree of alignment could also be determined using ImageJ software." Pet. 50. According to Petitioner, "if a [POSITA] wanted to perform an FFT analysis on the SEM image in Lee, a [POSITA] could do so using the ImageJ

software.... This would show the fibers were oriented on the scaffold in Lee in an aligned manner.” *Id.* Petitioner contends that a POSITA “would have been motivated to confirm the alignment of Lee’s fibers with a well-known established tool.” *Id.* at 51. Petitioner also contends that a POSITA would have expected success, as demonstrated by Dr. Simpson’s testing. *Id.* at 50-51. These arguments fail.

Petitioner fails to demonstrate a motivation to modify Lee. First, Petitioner applies the wrong standard in asserting that “*if a [POSITA] wanted to perform an FFT analysis on the SEM image in Lee, a [POSITA] could do so using the ImageJ software.*” Pet. 50. Petitioner must provide a sufficiently articulated reasoning with rational underpinning to explain why a POSITA *would have* “wanted to perform an FFT analysis” in the first place; that they *could* have done so *if* they wanted to is insufficient. “[C]ould have” is not the test. *Belden, Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (“Obviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.”); *Virtek Vision Int’l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 888 (Fed. Cir. 2024) (“It does not suffice to simply be known. A reason for combining must exist.”).

Moreover, Lee already confirms fiber alignment through three mechanisms *other than* FFT analysis: (1) scanning electron microscopy (SEM) examination,

(2) ImageTool 3.0 freeware analysis, and (3) tensile testing. Pet. 48-51. Petitioner fails to explain why a POSITA would have further confirmed alignment through a fourth mechanism. Pet. 50-51; *In re Magnum Oil Tools*, 829 F.3d at 1380 (“The petitioner must ... articulate specific reasoning.”).

For example, Petitioner does not show that a fourth confirmation mechanism based on FFT would have been needed, expected, or typical in the art. Pet. 50-51. Nor does Petitioner identify any deficiency in the three mechanisms Lee already used to confirm alignment. *Id.* Petitioner also does not contend that FFT analysis would have imparted a benefit over the mechanisms already employed. *Id.* This aspect of the prima facie case of obviousness must have been made in the Petition. CTPG 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”).

In fact, a POSITA would not have done so. Dr. Mikos testifies that, where alignment has already been confirmed, as in Lee, a POSITA would not expend more time or money to reiterate that finding. Ex. 2015 ¶ 158 (“It would be atypical to invest further time or money to reaffirm information that is already known.”). Moreover, Dr. Simpson testified that performing FFT on SEM images like Lee’s has known “disadvantages,” including that “it’s destructive.” Ex. 2017, 73:2-7. The Petition simply fails to establish that a POSITA would have undertaken FFT testing to reconfirm what was already established, especially in the face of increased cost

and time. *Edwards Lifesciences*, IPR2023-01232, Paper 10 at 36-37 (finding the purported motivation to be “inchoate” and “unpersuasive” because the “benefits” of the combination “are already conferred”); *UiPath, Inc. v.* IPR2024-01304, Paper 8 at 26-27 (finding no motivation to combine where the primary reference “already includes the option for the user to manually select a data source from a plurality of data sources” and petitioner and its expert offered only conclusory argument in support of its proposed combination).

Finally, Petitioner relies upon Dr. Simpson’s post-hoc testing to argue that a POSITA would have expected success. Pet. 50-51; Ex. 1003 ¶ 187. But obviousness concerns the time of invention, not the time an expert declaration is prepared. As such, Dr. Simpson does not establish that a POSITA *at the time* of invention would have expected success. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 974 (Fed. Cir. 2014) (“Obviousness, and expectation of success, are evaluated from the perspective of a person having ordinary skill in the art at the time of invention.”).

It was Petitioner’s burden to set forth its prima facie case of obviousness in the Petition itself. 35 U.S.C. § 312(a)(3). Petitioner may not advance a new theory of obviousness on Reply, CTPG 73, nor may the Board decide an obviousness case that was not presented in the Petition itself. *AMP Plus, Inc. v. DMF, Inc.*, 131 F.4th 1320, 1325 (Fed. Cir. 2025) (“[T]he law of obviousness does not require the court,

or the Board, to develop arguments for a limitation that the petition simply did not make.”).

Accordingly, Petition has not demonstrated that Lee renders obvious this limitation of claim 1.

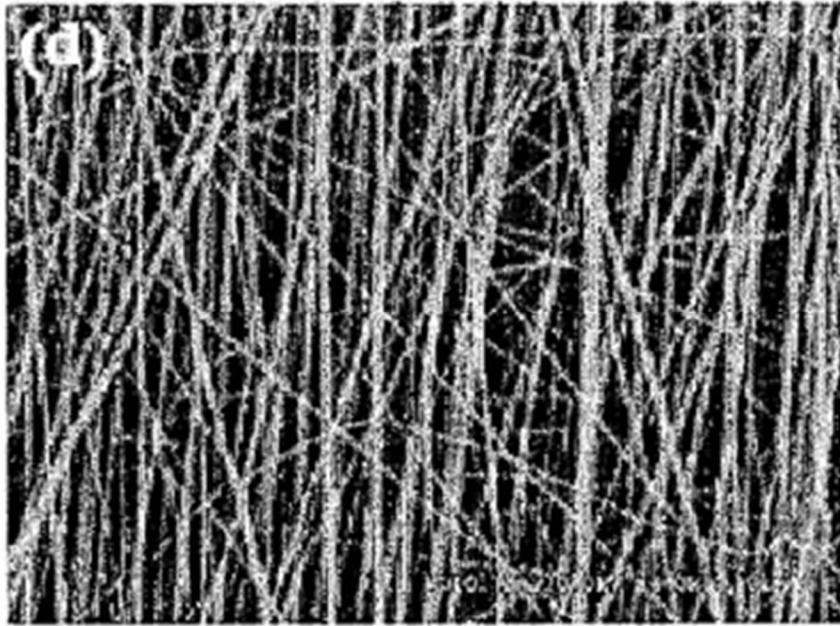
d) Dr. Simpson’s post-hoc FFT analysis is entitled to no weight

Dr. Simpson states that he “conducted [his] own analysis on Lee’s Figure 1D using the FFT analysis described in the ’227 patent.” Ex. 1003 ¶ 183. This is incorrect. Dr. Simpson’s testing is inconsistent with the ’227 patent.

(1) The tested image is different (and insufficient)

Dr. Mikos testifies that image quality is the single most important factor in FFT analysis. Ex. 2015 ¶ 162; Ex. 2017, 58:25-59:18, 142:14-15 (“You should always be collecting data with the best capability that you have.”). Without a sufficient image, FFT testing results cannot be credited. Ex. 2015 ¶ 162.

Dr. Simpson, however, did *not* test high quality images. Instead, Dr. Simpson performed FFT analysis on 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).



Ex. 1003 ¶ 179. Immediately apparent from visual inspection is this image's poor quality, with a facial lack of contrast between individual fibers, especially toward the background of Lee's scaffold. Ex. 2015 ¶ 164 (“[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.”). Performing FFT on such a reproduction can lead to invalid and inaccurate results. *Id.* ¶ 163. Indeed, Dr. Simpson himself has explained as much, stating that images “composed largely of optical noise,” like that depicted in the Lee provisional image above (*id.* ¶ 164), are “unsuitable for analysis” with FFT because “individual fibers are not detected.” Ex. 1010, 605.

Dr. Simpson testified that he “can see fibers” and “edges” in this photocopied image. Ex. 2017, 62:9-16. But, while some portions of this image may contain vaguely discernible fibers or edges, many other portions do not, with just one example shown below.



Ex. 1003 ¶ 184 (taken from the lower right portion of the image); Ex. 2015 ¶ 165 (explaining that “FFT analysis is useless on such an image because the individual fibers cannot be detected”). Dr. Simpson utterly fails to reckon with image quality or the extent of “optical noise” depicted here.

Dr. Mikos testifies that reproduced images like that used here introduce noise, blur, and uneven illumination to the analysis. Image contrast is reduced and fine details—essential to a reliable FFT result—are lost. Ex. 2015 ¶ 163; Ex. 1010, 609 (Dr. Simpson acknowledging that uneven illumination introduces error), 612 (Dr. Simpson acknowledging that noise introduces artifacts into the FFT result). Dr. Mikos testifies that the noise and artifacts introduced by testing of reproduced images adversely affects FFT plot shape with high frequency features, which reflect fiber orientation, most affected. Ex. 2015 ¶ 163.

Both Dr. Mikos and Dr. Simpson testified that they do not normally perform FFT analysis with reproduced or photocopied images for these very reasons.

Ex. 2015 ¶ 163; Ex. 2017, 157:8-14, 157:23-158:3.

(2) Lee's image was tested differently

Despite stating that he “us[ed] the FFT analysis described in the ’227 patent,” Ex. 1003 ¶ 183, Dr. Simpson did not. As an initial matter, Dr. Simpson’s declaration is incomplete and leaves out important details. Indeed, Dr. Simpson apparently applied a mask to Lee’s image but failed to disclose that in his declaration. *Compare* Ex. 1003 ¶ 125 (depicting a mask applied to Huang2’s image), *with id.* ¶ 179 (*not* depicting a mask applied to Lee’s image); Ex. 2017, 163:11-15 (“Q. Where in your report do you did discuss applying a mask to Lee? A. I’m sure it’s -- I would have thought it was here but it’s not.”).

This is doubly problematic. First, without documenting where or how Dr. Simpson applied a mask, his analysis cannot be evaluated. As discussed in his past publication, FFT analysis should occur over “as large as an area as possible” to avoid “bias[ing] the 2D FFT process.” Ex. 1010, 606. It is unclear how much of Lee’s image Dr. Simpson discarded in applying his mask. Ex. 2015 ¶ 168. Second, application of a mask is not “the FFT analysis described in the ’227 patent.” Specifically, the ’227 patent incorporates Dr. Simpson’s 2008 paper (Ex. 1010), but this paper discloses only an *optional* mask—an option that was not exercised in the ’227 patent. Ex. 1001, Fig. 8A (depicting the tested image without a mask).

As discussed above, inclusion or exclusion of a mask *directly* impacts the

resulting FFT plot. As Dr. Simpson previously published, for example, when performing FFT analysis on fibers oriented at 45°, the FFT plot includes “edge noise” that appears as small peaks in the FFT plot. Ex. 1010, 615. In particular, “[t]he unmasked image produces a 2D FFT alignment plot with artifacts in the guise of small peaks on either side of the alignment peaks (Fig. 3N, arrows). Processing the image with a window mask removes this spurious information without altering the height of the alignment peaks.” *Id.* In other words, inclusion of a mask is not a trivial detail and results in different peaks being included the FFT plot. Ex. 2015 ¶ 169; Ex. 1010, 615.

In sum, despite his statement to the contrary, Dr. Simpson did *not* perform the FFT analysis described in the '227 patent and, in doing so, also violated his own past statements regarding the importance of testing a sufficiently representative sample.

(3) Conclusion

Petitioner bears the burden of proving unpatentability by a preponderance of evidence. It cannot meet that burden by relying on poor quality photocopied images, tested in a manner that violates Dr. Simpson’s own past statements about the image quality necessary for FFT analysis. Lee’s image consists largely of optical noise and is “unsuitable for analysis” with FFT because “individual fibers are not detected.” Ex. 1010, 605. Dr. Simpson’s current claim that Lee’s image is sufficient for such testing is self-serving and simply not credible. *Wilson v. Martin*, 789 F. Appx. 861,

870 (Fed. Cir. 2019) (“The purpose of extrinsic evidence in an anticipation analysis ‘is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, *not to fill gaps in the reference.*’”) (emphasis added).

e) The FFT protocol is insufficiently explained

With this background of omission and inconsistency, Dr. Simpson’s statement that he “conducted [his] own analysis on Lee’s Figure 1D using the FFT analysis described in the ’227 patent” is insufficient to satisfy 37 C.F.R. § 42.65(b). *Luitpold Pharms.*, IPR2018-01640, Paper 19 at 23-24.

As discussed above, a POSITA typically documents the steps taken in performing FFT analysis. Ex. 2017, 59:19-60:8; Ex. 2015 ¶ 170. Dr. Simpson’s declaration, however, does not even identify something as critical as the presence of a mask applied to the tested image. Ex. 2017, 163:11-15. Nor does Dr. Simpson recall the *version of software* he used, let alone the parameters he applied. Ex. 2017, 140:24-141:4. Likewise, Dr. Simpson did not document where or how he applied the circular projection in the ImageJ software to his FFT output image to generate his FFT plot, a “critical” aspect of FFT analysis. Ex. 2015 ¶ 172 (“If the circular selection does not capture a representative portion of the FFT output image, it will bias the results.”). In this vacuum, reproducing his testing is impossible.

In addition to the inconsistencies discussed above, Dr. Simpson’s earlier

paper, incorporated by reference into the '227 patent, describes other critical aspects of FFT analysis that are essential, but are not accounted for in Dr. Simpson's testing, and which *directly impact* both the validity of FFT testing and the shape of the resultant FFT plot. Ex. 2015 ¶ 165. For example, Dr. Simpson emphasizes the importance of image quality to reliable FFT testing. In his 2008 paper, Dr. Simpson utilized images that were "stored and analyzed as uncompressed .TIF files to preserve image integrity [because] the image compression used in .JPG format will degrade image integrity." Ex. 1010, 607. In his post-hoc testing, however, Dr. Simpson "ha[d] no idea" how Lee's image was stored and did not attempt to account for that in his analysis. Ex. 2017, 160:23-161:2.

Again, it was Petitioner's burden to demonstrate anticipation; that burden cannot be satisfied with incomplete post-hoc testing that violates 37 C.F.R. § 42.65(b). Dr. Simpson's results cannot be credited.

3. Lee lacks the "repair [of] a tendon, a ligament or a nerve defect"

Petitioner acknowledges that "Lee does not expressly disclose ... repair[ing] a tendon, ligament, or nerve defect," but asserts this would have been obvious "given the similarities between the tissue" types. Pet. 51-52.⁹ Petitioner's reasoning fails.

⁹ Petitioner's reliance on Kuo is addressed below regarding the alternate allegation

Lee involves muscle tissue repair, achieved by seeding Lee's scaffold with human skeletal muscle cells ("hSkMCs"), which "fuse[] and form[] myotubes." Ex. 1011 ¶¶ 2, 31, 60, 72-73, 82. Lee does not repair any other tissue type. A POSITA would not have utilized Lee's scaffold to repair the claimed tissues because it is *only* suitable for muscle repair. As explained below, Lee's scaffold is seeded only with muscle cells and presents an elastic modulus that is insufficient to repair the claimed structures. Ex. 2015 ¶ 177; *infra* § V.C.4.b (incorporated herein by reference).

Dr. Simpson's testimony that "Lee's scaffold ... could also have been used to treat" other tissues, Ex. 1003 ¶ 188, is beside the point. The proper inquiry is whether a POSITA *would* have been motivated to do so with a reasonable expectation of success. *Belden*, 805 F.3d at 1073. The Petition does not present any reasoning *why* a POSITA would have used Lee's muscle scaffold to repair non-muscle tissues. Pet. 51-52 (simply stating that it "could" be done). And, as detailed *infra*, a POSTA would not have done so. Petitioner does not meet its burden.

of obviousness based on Lee and Kuo, and those arguments are incorporated herein. *Infra* § V.C.4.

4. Lee and Kuo do not render obvious the “repair [of] a tendon, a ligament, or a nerve defect”

Alternatively, Petitioner alleges a POSITA would have used Lee’s scaffold to repair a tendon, ligament, or nerve defect, as suggested by Kuo. Pet. 52-54.¹⁰ Petitioner alleges the references are in “the same field of art, and both seek to solve the same problems” related to the creation of aligned scaffolds that mimic native tissue. *Id.* at 52. These arguments fail.

a) Common fields or problems are not sufficient

A common field of art and/or problem to be solved does not constitute articulated reasoning with rational underpinning as to *why* a POSITA would have modified Lee with Kuo. *Supra* § V.B.4.a (incorporated by reference).

b) Lee is incapable of repairing tendon, ligament, or nerve

Petitioner errs in treating Lee and Kuo as interchangeable merely because both teach scaffolds with aligned fibers. Petitioner overlooks dispositive differences that demonstrate the references would not have been combined. Pet. 52-54.

¹⁰ The cited publication by Lanza and Alta, Pet. 53, is not attached as an exhibit. 37 C.F.R. § 42.6(c).

(1) Kuo requires a jelly-roll configuration

Kuo treats tendon, ligament, and nerve defects with a unique “jelly-roll” scaffold, that allegedly presents advantages over non-rolled scaffolds like Lee’s. *Supra* § V.B.4.b.1 (incorporated by reference). Lee does not disclose a rolled scaffold, and Petitioner does not propose modifying Lee to present that essential structure. Pet. 52-54.

For the reasons articulated above, a POSITA would not have utilized Lee’s unmodified scaffold to repair tendon, ligament, or nerve tissue because Lee lacks the unique rolled, three-dimensional structure taught by Kuo that mimics the structure of tendon, ligament, or nerve fascicles. Ex. 2015 ¶¶ 178-179; Ex. 1018 ¶ 5. That Kuo utilizes aligned fibers in some embodiments does not demonstrate obviousness. Kuo relies primarily upon its rolled structure; aligned fibers are utilized in *some* embodiments but are an optional and secondary feature. For example, Kuo’s fibers may be aligned, random, or a combination, but Kuo requires that the scaffold be rolled to repair these tissues. *E.g.*, Ex. 1018 ¶¶ 5, 12, 34.

Although “Kuo specifically discloses that its scaffolds can be used to treat muscle injuries, which is also the focus of Lee,” DI 40, Kuo makes clear that its treatment of muscles, tendons, ligaments, and nerves employs a unique rolled design that is absent in Lee. Ex. 1018 ¶¶ 5, 6, 23, 34. Indeed, it is this rolled design that Kuo states, “form[s] structures similar to the fascicles of the muscle” and avoids

problems of poor cell seeding present in non-rolled aligned scaffolds like Lee. *Id.* ¶¶ 5, 112; *id.* ¶ 6 (“Compositions described herein mimic native tissue structure by forming individual engineered fascicles, which are considered sub-components of whole muscle, nerve, tendon, and ligament tissues, and by forming whole tissues comprised of bundled engineered fascicles.”); Ex. 2015 ¶¶ 178-179.

Thus, although both Lee and Kuo use scaffolds for muscle repair, Kuo limits that use—and that of tendon, ligament, and nerve—to treatment with a rolled scaffold. It does not follow that “a POSITA would also be motivated to utilize[] the aligned scaffolds taught in Lee to treat the other types of tissues identified in Kuo,” DI 40, when Kuo requires a rolled structure that is absent in Lee. Ex. 2015 ¶ 179. Petitioner does not demonstrate that a POSITA would have sought to treat those same tissues with Lee’s different, non-rolled scaffold. *Id.*

Nor does Petitioner propose to modify Lee’s scaffold by rolling it. And had it been proposed (it was not), a POSITA would not have done so because of well-documented drawbacks of rolled scaffolds, discussed above regarding Ground 1, which apply equally here. *Supra* § V.B.4.b.1; Ex. 2015 ¶¶ 180-181; Ex. 2022, 3:54-4:9, 5:39-46 (explaining that rolled structures fail to mimic natural nerve growth, contain seams that result in weak connective points, cause axons to grown in a “jumbled disorganized mass,” and allow for infiltration by unwanted cells).

(2) Lee's elastic modulus is insufficient

As discussed above regarding Ground 1, incorporated herein, the elastic modulus of a tissue repair scaffold must mimic that of native tissue. Ex. 2015 ¶ 183; Ex. 2024, Abstract (“Naive mesenchymal stem cells (MSCs) are shown here to specify lineage and commit to phenotypes with extreme sensitivity to tissue-level elasticity.”). Lee does not disclose its scaffold’s elastic modulus value, but muscle tissue has a very low elastic modulus, ranging between 0.00096-0.00501 MPa, and a POSITA would understand that a muscle tissue scaffold like Lee’s would present an elastic modulus value that mimics that of native muscle tissue. Ex. 2015 ¶¶ 129, 184; Ex. 2025, 1548. The elastic modulus of tendon and ligament vary markedly from those values, ranging up to 660 and 447 MPa, respectively. Ex. 2015 ¶ 185; Ex. 2026, 801; Ex. 2028, 429. A POSITA would not have utilized Lee’s muscle scaffold to repair these tissues, which require *over 687,500 and 465,625-times* greater stiffness, respectively. Ex. 2015 ¶¶ 186, 188.

Likewise, the elastic modulus of nerve tissue (up to 0.019 MPa) is also higher than that of muscle, by a magnitude of *19 times*. *Id.* ¶¶ 129, 187-188. Lee’s scaffold would be too compliant to perform the required functions for tendon, ligament, and nerve repair. *Id.*; *supra* § V.B.4.b.2 (incorporated by reference).

(3) Lee's structure and seeded cell are insufficient

As discussed above in Section V.C.3, Lee exclusively repairs muscle tissue

using scaffolds seeded with human skeletal muscle cells (“hSkMCs”)—cells unique to muscle. Ex. 1011 ¶¶ 72-73; Ex. 2015 ¶ 190. Lee does not repair any other tissue type.

Petitioner paints with too broad a brush in suggesting that Lee and Kuo are interchangeable merely because they both disclose aligned fibers. To the contrary, *supra* § V.B.4.b.3 (incorporated herein), the cell types seeded on each scaffold differ, which dictates the type of tissue that may be repaired with that scaffold. Ex. 2015 ¶¶ 190-191. Likewise, as discussed above, the scaffold’s degradation rate and stiffness must be matched to that of tendon, ligament, and nerve tissue to successfully repair those tissues. *Id.* ¶ 192. A POSITA would not expect Lee’s scaffold, seeded with hSkMCs and with an elastic modulus likely matched to muscle tissue, to successfully promote tendon, ligament, or nerve repair because it is devoid of the cell type and scaffold structure needed to repair those tissue types. *Id.* ¶ 193.

As above, the Petition does not explain how, e.g., tendon tissue would have been repaired with Lee’s hSkMCs-seeded scaffold. To the contrary, Kuo demonstrates that when tendon repair is intended, the scaffold is seeded with *tendon* cells (tenocytes) or stem/progenitor cells that differentiate into tendon tissue. Ex. 1018 ¶¶ 16, 112; Ex. 2015 ¶¶ 191-193. Nor does the Petition propose modifying Lee’s scaffold to incorporate alternate cell types or appropriate scaffold structure.

Accordingly, Petitioner fails to demonstrate that a POSITA would have used Lee's muscle repair scaffold, seeded with hSkMCs, to repair different tissue types as taught by Kuo. The record demonstrates that use of Lee's scaffold as proposed would not have been successful, for example, in the absence of seeded cells specific to those tissues. Ex. 2015 ¶¶ 193-194.

(4) Muscle differs markedly from tendon, ligament, and nerve

Although Kuo teaches repair of muscle tissue as well as tendon, ligament, and nerve, those four tissues vary. *Supra* § V.C.4.b. Muscle tissue is a highly vascularized tissue with abundant blood supply as compared to tendon, ligament, or nerve tissue. Ex. 2015 ¶ 196; Ex. 2034. The low vascularity of tendon, ligament, and nerve tissue affects their ability to be repaired with a tissue scaffold like Lee's. *Id.* Accordingly, Dr. Mikos testifies that a POSITA would recognize that, although Lee and Kuo both repair muscle tissue, Lee's scaffold would not have been used to alternatively repair tendon, ligament, or nerve tissue because, among other difference discussed above, those tissues also lack the vascularity that contributes to Lee's successful repair of muscle tissue with its disclosed scaffold. Ex. 2015 ¶¶ 196-198. A POSITA would not have expected success in utilizing Lee's scaffold to repair tendon, ligament, or nerve tissue due, in part, to the drastically different vascularization of those tissues. *Id.*

5. Dependent claims 2-6 would not have been obvious

Dependent claims 2-6 include all limitations of independent claim 1 and, accordingly, Petitioner's contentions likewise fail.

a) Claim 2

Dependent claim 2 further recites that "the scaffold is in the form of one or more elongated sheets." Ex. 1001, 23:38-39. Petitioner relies upon Lee and, alternatively, Kuo as both disclosing a scaffold sheet. Pet. 54.

Lee describes its scaffold as "an array of natural or synthetic matrix molecules to which cells or fibers can attach" or a "mesh." Ex. 1011 ¶¶ 44, 45. As with Ground 1, which arguments are incorporated by reference, this ground turns on the combination of Lee and Kuo. As discussed above, Kuo repairs tendon, ligament, or nerve, with a spirally wound jelly-roll structure. *Id.* at Fig. 1. A roll is not a sheet, as a POSITA would understand the term. Ex. 2015 ¶¶ 202-204; Ex. 2032, S22; Ex. 2033, 1632; Ex. 2017, 194:5-8.

Petitioner's contention that a POSITA would have been motivated to use a sheet is nonsensical, given the Petition's reliance upon Kuo to teach the repair of tendon, ligament, or nerve. Pet. 54. The Petitioner does not provide *any* reason why. *Id.*; Ex. 1003 ¶¶ 199-204. Petitioner and Dr. Simpson simply conclude that a POSITA "would have been motivated with a reasonable expectation of success" without answering the most important question: "why?" or "how"? Pet. 54 (where

all citations also fail to disclose motivation). Simply put, there is no such motivation, where Kuo's repair turns on the presence of a rolled scaffold that mimics tendon, ligament, or nerve.

b) Claim 3

Dependent claim 3 further recites that “the scaffold is a composite of multiple layers of one or more sheets.” Ex. 1001, 23:40-41. Petitioner alleges that Lee “form[s] a multilayer polymeric matrix structure,” and that Kuo teaches “multiple ‘sheets’ in the scaffold.” Pet. 54-55. Petitioner also alleges that multi-layered sheets were well known and that a POSITA “would have been motivated ... to use Lee’s aligned fibers in scaffolds in the form of multiple layers of one or more sheets as disclosed by Kuo.” *Id.* at 55-56.

The arguments against claim 2 are incorporated herein. Kuo teaches a rolled scaffold to treat the claimed tissues, not one or more sheets. Ex. 2015 ¶ 206. As discussed regarding Ground 1, which arguments are also incorporated herein, Kuo does not disclose a composite of multiple layers; instead, Kuo simply uses the plural form of the term “sheet.” Ex. 1018 ¶¶ 24, 34; Ex. 2015 ¶ 207. Moreover, even if “multi-layer sheets” were “used extensively in the scientific literature,” Pet. 55, Petitioner does not explain *how or why* a multi-layer sheet would have been employed in the rolled scaffold taught by Kuo. Pet. 55.

c) Claims 4, 5, and 6

Dependent claims 4, 5, and 6 further specify that “the tissue defect is” a nerve defect, ligament defect, or tendon defect, respectively. Ex. 1001, 23:42-24:4. As discussed above regarding claim 1, the combination of Lee and Kuo does not render obvious the treatment of these specific tissue defects. Lee scaffold, seeded with human skeletal muscle cells and with a Young’s modulus that matches that of muscle tissue, is not applicable to the repair of nerve, ligament, or tendon defects as taught by Kuo, which entails use of a rolled scaffold. Ex. 2015 ¶ 209.

D. Ground 3: Huang2 does not anticipate claims 7-8

Independent claim 7 also recites “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. Petitioner alleges that Huang2 discloses this limitation, as set forth for Ground 1. Pet. 60-61. For the reasons discussed above, expressly incorporated herein by reference, Petitioner’s contentions fail. *Supra* § V.B.2-3.

VI. CONCLUSION

Patent Owner submits that Petitioner has not met its burden to prevail on any claims challenged in this *inter partes* review.

Dated: October 29, 2025

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Certification under 37 C.F.R. § 42.24(d)

I hereby certify that this response, excluding its table of contents, table of authorities, certification under 37 C.F.R. § 42.24(d), certificate of service, and appendix of exhibits has 13,971 words as counted by Microsoft Word, the word-processing system used to prepare this preliminary response.

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Certification of Service

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on October 29, 2025, a copy of the foregoing document and attached exhibits were served by electronic mail upon the following counsel of record for Petitioner:

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