

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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

v.

LIFENET HEALTH,  
Patent Owner.

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

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**PATENT OWNER'S SUR-REPLY**

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| Ex.# | 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                                                                                                                                                                                                                                                                                                        |
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| 2010 | Webpage, Tapestry® RC Biointegrative Implant System ( <a href="https://www.zimmerbiomet.com/en/products-and-solutions/specialties/sports-medicine/tapestry-rc-biointegrative-implant-system.html">https://www.zimmerbiomet.com/en/products-and-solutions/specialties/sports-medicine/tapestry-rc-biointegrative-implant-system.html</a> )         |
| 2011 | Webpage, ActivBraid® Collagen Co-Braid ( <a href="https://www.zimmerbiomet.com/en/products-and-solutions/specialties/sports-medicine/activbraid.html">https://www.zimmerbiomet.com/en/products-and-solutions/specialties/sports-medicine/activbraid.html</a> )                                                                                    |
| 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 ( <a href="https://web.archive.org/web/20250512015553/https://embody-inc.com/our-technology/">https://web.archive.org/web/20250512015553/https://embody-inc.com/our-technology/</a> )                                                                                                           |

| Ex.# | Description                                                                                                                                                                                                                        |
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| 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")                                    |

| Ex.# | Description                                                                                                                                                                         |
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| 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”)                                      |
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## I. INTRODUCTION

Petitioner's Reply doubles-down on the premise that the claims simply require "aligned fibers." But this is not recited. Instead, independent claim 1 requires crosslinking, a specific FFT analysis result having "major adjacent peaks," and tendon/ligament/nerve treatment. It recites:

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.

Ex.1001, 23:29-37.

The Petition's grounds fail for six reasons. First, Huang2 lacks crosslinked fibers. Second, Huang2 lacks the claimed FFT analysis result having "major adjacent peaks," under the Specification's lexicographic definition and Petitioner's proposed construction. Third, Lee does not disclose FFT analysis results at all, and the Petition fails to demonstrate inherency. Fourth, treatment of tendon, ligament, or nerve would not have been obvious over either Huang2 or Lee, with Kuo, due to multiple structural differences. Fifth, Petitioner propounds unreliable expert testing and improper new Reply theories. And sixth, dependent claims 2-6 stand independently on their own merits.

## II. ARGUMENT

### A. The Specification lexicographically defines “major peaks”

Fiber alignment impacts scaffold properties. Pet. 8. FFT analysis evaluates that alignment and generates a result where “the shape of its peaks indicat[e] the extent of alignment.” *Id.* 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” and depicts “fibers that present additional orientations” as “smaller or minor peaks.” Ex.2015 ¶¶58-59; Ex.1010, 610.

The '227 patent claims its electrospun scaffold very specifically. It did not recite “aligned fibers,” a term Petitioner fails to define with any precision. Instead, it claimed a specific FFT result having “major adjacent peaks that are about 180° apart from each other.” Ex.1001, 23:32-34. And the Specification expressly defined “major peaks.”<sup>1</sup> Petitioner does not dispute that the Specification presents the hallmarks of lexicography. Instead, Petitioner argues the definition—“‘major peaks’ herein refer to peaks higher than the average of the peaks in the result”—is unclear because the “multi-step numerical procedure” for “calculat[ing] an arithmetic mean”

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<sup>1</sup> Petitioner argues “‘major adjacent peaks’ ... is not defined.” Reply 3. The adjective “adjacent” within the defined phrase does not alter its definition. Petitioner provides no evidence a POSITA would understand these phrases differently.

is undescribed. Reply 3-4; Ex.1001, 13:28-29.

This fails. Petitioner defines a POSITA as a two-year Ph.D. student who understands mathematical FFT analysis. Pet. 20-21. No evidence suggests this highly-skilled POSITA needed a detailed explanation to calculate an average – a skill taught in grade school. The absence of testimony from Dr. Simpson is telling. Ex.1220, 64:1-17 (Dr. Mikos stating a POSITA could do so).

Moreover, the Petition recognized and accepted the Specification's definition. Pet. 11 (“According to the specification, ‘the [‘]major peaks[’] ... refer to peaks higher than the average peaks in the result.”). Any argument that this definition is inapplicable or unclear was required in the Petition. Pet. 21 (no construction); 37 C.F.R. §42.104(b)(3).

**1. This construction is supported by the intrinsic record**

**a) Specification**

Figure 8A, the preferred embodiment, depicts “major peaks” as defined:

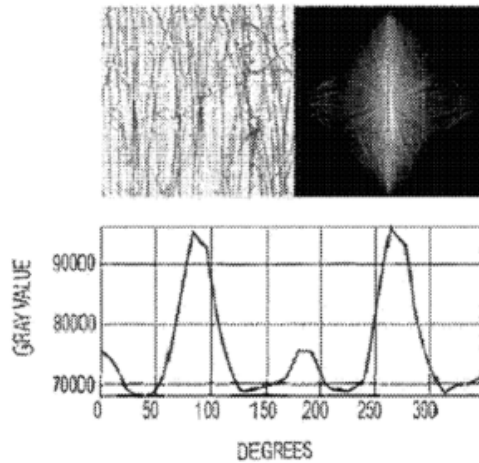


**FIG. 8A**

Ex.2015 ¶57 (major peaks at 90°/270°).

By contrast, Figure 8B depicts a “control” sample of random fibers, where no peaks exceed the average height (within conventional bounds of experimental error).

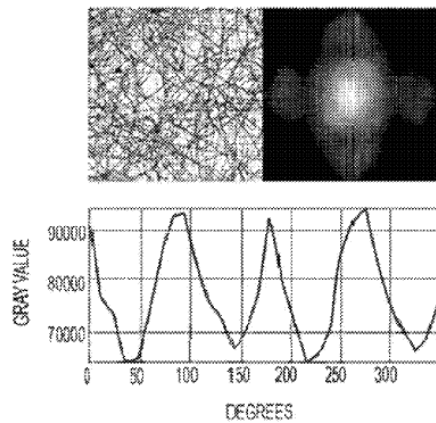


**FIG. 8B**

Ayres-2008, incorporated by reference, likewise explains, “peaks of nearly uniform

height”—like Figure 8B—indicate a random scaffold.<sup>2</sup> Ex.1010, 609; Ex.2017, 88:7-15 (Dr. Simpson explaining the lack of major peaks where “all the peaks ... look like they’re essentially very similar in height”).

Petitioner contends Figure 8B violates the lexicographic definition because the 90°/270° peaks appear fractionally higher than average, implying that a FFT result of random fibers requires identical peak heights, contrary to Dr. Simpson’s earlier statements. Reply 7-8. Not so.

First, the Specification is silent regarding peak height and Figure 8B “is not very clear” such that peak height can only be “guesstimate[d].” Ex.1220, 69:25-70:7. Although Dr. Simpson alleges that the 90°/270° peaks exceed the average by 820/1790 units (out of ~95,000), he does not argue this presents any statistical significance. Ex.1219 ¶19.<sup>3</sup> This contrasts with Figure 8A, where the 90°/270° peaks plainly exceed the average, even accepting some “guesstimat[ion]” or measurement error. Ex.2015 ¶57 (“approximat[ing]” heights; exceeding average by 10,000 units); Ex.1220, 63:16-18.

Second, Dr. Mikos testifies that, in a FFT plot, “what appears at 0 degrees

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<sup>2</sup> Unless noted, emphasis added/internal citations omitted.

<sup>3</sup> These deviations must be statistically insignificant to align with his testimony that FFT peaks “repeat between 0°-180° and 180°-360°.” Ex.1003 ¶47.

would appear at 360 degrees”; it is “the same peak.” Ex.1220, 62:17-20. But Figure 8B is “cut at 350<sup>[o]</sup>”; one “cannot clearly see where it goes” or “where it ends at ... 360 degrees.” *Id.* 66:18-22 (“I wanted to see it at 360 degrees.”); Ex.1001, Fig.8B (discontinuous after 350°). The 0°/360° peak’s apex/height is not depicted; Dr. Simpson simply speculates. Ex.1220, 69:15-19 (Dr. Mikos stating the 0°/360° peak is “above 90,000. Whether it’s 91,000, 92,000, 93,000, I cannot tell.”).

Finally, whether Ayres-2008 supports this construction is irrelevant. Reply 5-8. Ayres-2008 is incorporated to explain how “FFT analysis may be performed,” but the claims recite a specific FFT result defined by the patent. It is perfectly reasonable to incorporate Ayres-2008 for background knowledge while claiming a specifically defined embodiment.

#### **b) Prosecution history**

Petitioner improperly relies upon the applicant’s silence during prosecution of the parent patent application. Reply 8-9. But “an applicant’s silence regarding statements made by the examiner during prosecution, without more, cannot amount to a ‘clear and unmistakable disavowal’ of claim scope.” *Salazar v. Procter & Gamble Co.*, 414 F.3d 1342, 1344-1345 (Fed. Cir. 2005).

#### **2. This construction is supported by a POSITA’s understanding**

Dr. Mikos explains that this definition aligns with a POSITA’s understanding.

Ex.2015 ¶¶58-59.<sup>4</sup> Dr. Simpson agreed:

Q: “Would another way to describe a major peak be that its height is higher than the average heights of the peaks in the plot?”

A: “If a user so desired, yes.”

Ex.2017, 89:3-6.

Whether the prior art calculates an average is inapposite. Reply 11-12. The patentee acted as lexicographer and may “use terms in a manner other than their ordinary meaning.” *Vitronics Corp. v. Conception, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).<sup>5</sup>

**a) Minor peaks are required**

To be clear: the claimed FFT result must have smaller/minor peaks; this is definitionally required to obtain an average height that is exceeded by “major peaks.” Reply 4; Ex.2015 ¶59. This reflects real-world scaffolds where “high

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<sup>4</sup> Petitioner misrepresents Dr. Mikos experience. Reply 10. Dr. Mikos performed FFT, including to determine alignment, and taught courses covering FFT. Ex.1220, 31:1-32:20, 34:5-11; 35:2-6.

<sup>5</sup> There is no inconsistency with Patent Owner’s district court pleadings. Reply 19. Petitioner points to the Complaint, which quotes Petitioner’s product description. Ex.2005 ¶¶49-52. Neither infringement nor claim construction positions have been exchanged.

frequency signals” that “reflect fiber alignment” are plotted as “prominent or ‘major’ peaks,” and where “fibers that present additional orientations” are plotted as “smaller or minor peaks.” Ex.2015 ¶¶58-59; Ex.1001, Fig.8A.<sup>6</sup>

**b) Noise is not a “peak”**

Petitioner wrongly argues this definition “limits the claims to FFT plots that contain noise or imperfections.” Reply 7. Not so.

FFT peaks reflect alignment. Ex.2015 ¶¶58-59; Ex.1010, 610. Figure 8A’s FFT result depicts primary fiber alignment with major peaks and secondary alignment with minor peaks.

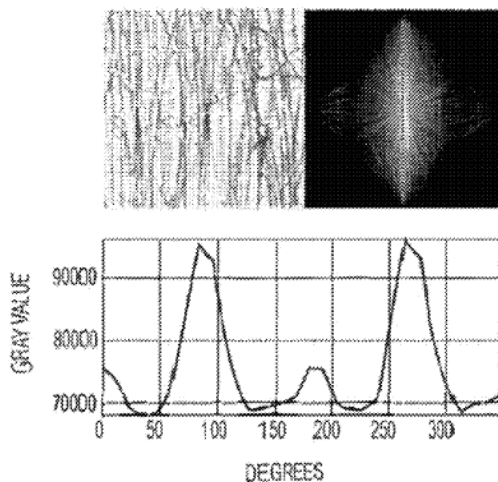


**FIG. 8A**

Figure 8A’s SEM image confirms this. Ex.1220, 77:14-78:24 (Dr. Mikos explaining

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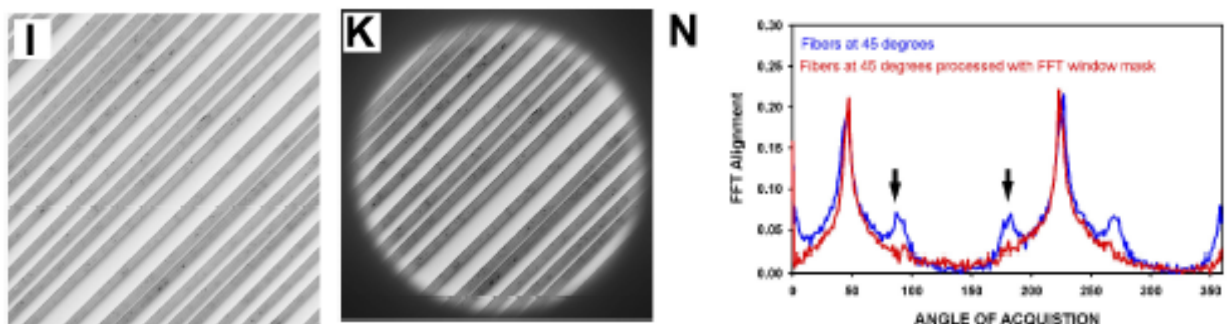
<sup>6</sup> This contrasts with Ayres-2008’s perfectly aligned spaghetti. Ex.1010, 606, 614.

the 0°/180° peaks “represent a secondary axis of alignment ... especially when I see the top left [SEM] image”).

Noise, by contrast, typically reflects ambient conditions. Ex.2017, 108:19-116:1 (Dr. Simpson giving noise examples, e.g., detector variation, electrical surges, imaging parameters, “ghosts in the machine”). As Dr. Simpson explains: “‘Noise’ is something that’s usually nonconsistent”; “Electronic noise is certainly random.” *Id.* 112:19-20, 113:25.

Both experts agree noise is depicted as small “movement of the [FFT trace] line up and down.” Ex.1220 (Mikos), 83:3-4, 81:16-19; Ex.2017 (Simpson), 114:17-115:2, 115:23. Because noise does not reflect alignment, Dr. Mikos testifies that “any [FFT] spikes that are part of noise” are not “peaks.” Ex.1220, 81:9-11, 75:10-76:14, 78:7-11; Ex.1010, 608 (“[P]eak shape and height ... report ... alignment.”). Similarly, Dr. Simpson explains that because noise and artifacts “can ‘spill over’ and obscure [FFT alignment] data,” it can be removed. Ex.1010, 615.

The Reply argues that the “major peaks” definition is “nonsensical” based on Ayres-2008’s Figure 3N:



Reply 6-7. Petitioner is wrong.

In Figure 3N, the blue FFT trace reflects Figure 3I's image and the red trace reflects Figure 3K's. Ayres-2008 explains that the positioning of "aligned fibers ... arrayed approximately 45° with respect to the border of the image," i.e., Figure 3I, creates edge effect artifacts that add "spurious information" to the FFT result (arrows). Ex.1010, 613, 615. Because this "spurious information" can be removed by masking, i.e., Figure 3K, Petitioner argues that "the accurate red trace would fall outside the claims, while the noisy blue trace would fall within them." Reply 6.

But this is incorrect; neither the red nor the blue trace fall within the claims because neither has "major peaks." Ex.1010, 613-614. The "spurious information" identified in the blue trace does not reflect fiber alignment; Dr. Simpson explains these artifacts are caused by the fibers' position relative to the image border. *Id.* 613.<sup>7</sup> They are not "peaks" included in the average peak height.

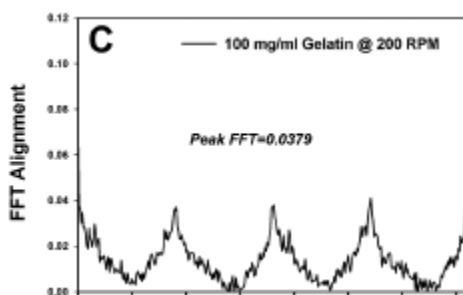
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<sup>7</sup> This "spurious information" exists only because the image violates proper positioning. Ex.1010, 607 (explaining the principal axis of alignment should be oriented at 90°, i.e., vertically; "[a]ngle information concerning the principle direction of fiber alignment must be calibrated. Convention places ... 90° at 12:00"); Ex.1013, 4.

### 3. Petitioner's construction has the same effect

Ignoring this definition, Petitioner construes “major peaks” as requiring a “qualitative” and “visual assessment of the relative sizes of the peaks to determine which peaks are ‘major.’”<sup>8</sup> Reply 5. But a FFT result with peaks of identical height also lacks “major peaks” under Petitioner’s construction because a “qualitative” and “visual assessment of the relative sizes of the peaks” demonstrates they are identical; neither is “major” when visually assessed “relative” to the other.

Dr. Simpson similarly testifies that, in the FFT result below, he “would not refer to that [peak at 90°] as a major peak because all the peaks ... look like they’re essentially very similar in height.”



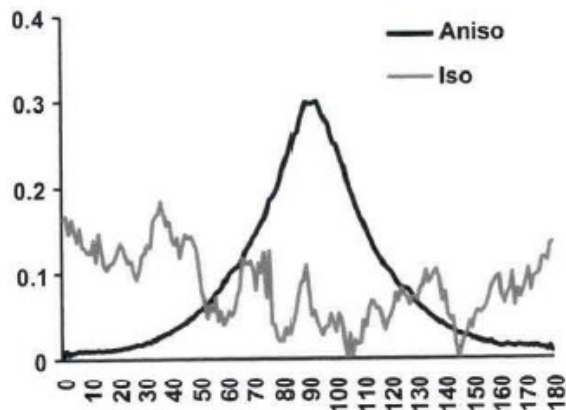
Ex.2017, 88:7-15.

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<sup>8</sup> Ayres-2008 does not qualitatively identify major peaks; it quantifies “alignment value,” i.e., peak height. “The overall 2D FFT alignment value for a scaffold is determined by visually inspecting and selecting the maximal value from the peak.”

Ex.1010, 613.

The implications of this qualitative visual assessment apply directly to Huang2, below.



Ex.1005, Fig.1C. Assuming *arguendo* that a second, identical peak appears between 180°-360°, both peaks present a 0.3-unit height. A qualitative “visual assessment of the relative sizes of the peaks” dictates that neither is major because there is no relative size difference. Reply 5. In Dr. Simpson’s framing, “all the peaks ... look like they’re essentially very similar in height.” Ex.2017, 88:7-15.

## **B. Huang2/Kuo do not render obvious claim 1**

### **1. Huang2 lacks “crosslinked fibers”**

That crosslinking is “one method to improve stability” does not establish that a POSITA would have crosslinked Huang2’s fibers, where stability was already achieved through blending. Reply 20; Ex.1005, 1791-1792. Petitioner does not allege that Huang2’s blended fibers are insufficiently stable or would have benefited from crosslinking in another way. Reply 20-21; Resp. 13-17. It is insufficient to simply allege that Huang2’s fibers could have been crosslinked. *Virtek Vision Int’l*

*ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 888 (Fed. Cir. 2024) (“A reason for combining must exist.”).

Whether Lee or Meniel employ crosslinking is irrelevant because their fibers differ significantly from Huang2’s. Lee discloses a 1:1 PCL/collagen blend lacking the high PCL level (3:1) that stabilizes Huang2. Ex.1011 ¶¶63; Ex.1220, 188:20-24 (it “is very important to consider ... the relative amount of collagen to PCL” in Lee).<sup>9</sup> And unlike Huang2, Meinel does not blend collagen at all. Ex.1023, Abstract.<sup>10</sup>

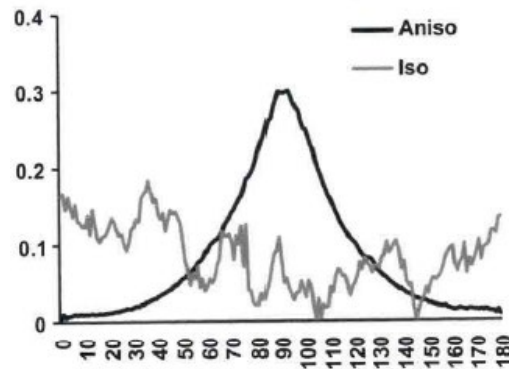
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<sup>9</sup> Collagen can be crosslinked but PCL cannot, Ex.1220, 187:11-17, further confirming a POSITA would not crosslink Huang2, which contains three-times more PCL than collagen. Ex.2015 ¶¶63-71.

<sup>10</sup> Kuo incorporates Meniel regarding scaffold “structural format,” e.g., “nanoscale diameter fibers from electrospinning, fiber bundles and films,” not crosslinking. Ex.1018 ¶40.

## 2. Huang2 lacks “major adjacent peaks”

Huang2’s FFT result lacks “major adjacent peaks,” of independent claims 1 and 7.



Because a single peak is disclosed, that sole peak controls the average height of all peaks in the result, even if a second identical peak appears between 180°-360°. This peak height *is identical to* the average; it is not higher and, definitionally, is not a “major peak.” Ex.2015 ¶¶76-77; Ex.1220, 79:9-13 (Dr. Mikos: “If I had two peaks ... [having] the same height, I would not consider those as major peaks.”).

Huang2 lacks “major peaks” even under Petitioner’s construction. §II.A.3.

## 3. Dr. Simpson’s testing is insufficient

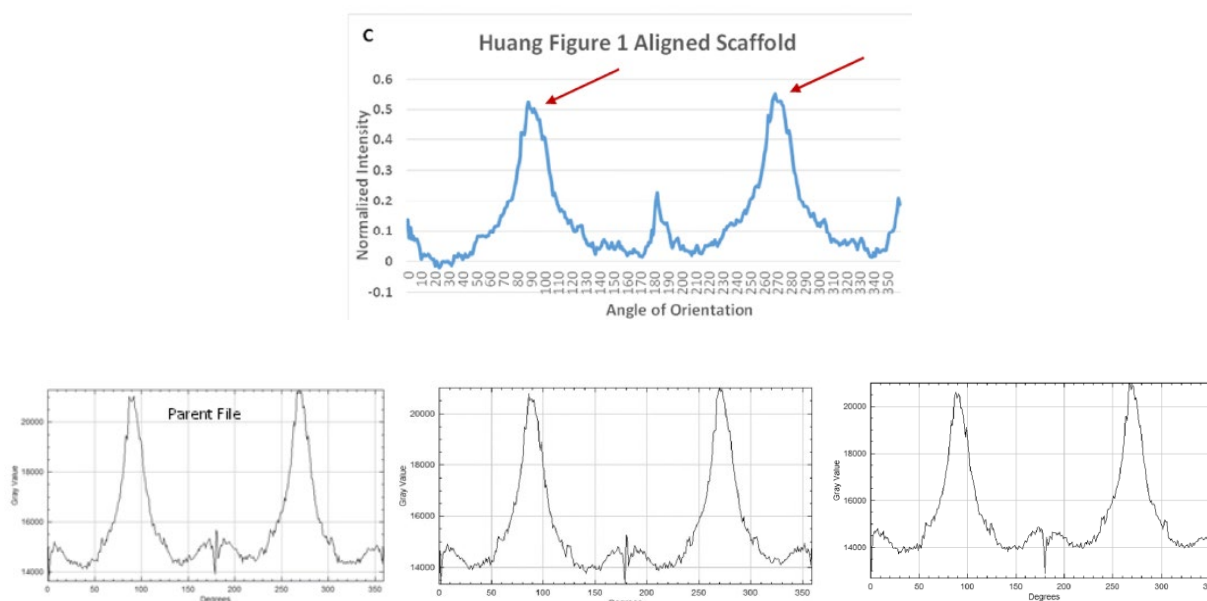
### a) It is inconsistent with Huang2

Petitioner relies upon FFT testing performed by Dr. Simpson. As discussed in the Response, Dr. Simpson performed a *different* analysis than Huang2 (among other deficiencies). Resp. 20-28. Dr. Simpson misunderstood Huang2’s disclosure and mistakenly applied a mask that Huang2 did not use. Ex.2017, 144:11-13,

146:11-12 (“I used a circular mask because I misread that sentence.”).

Recognizing this error, Dr. Simpson provides a supplemental declaration with new testing. Ex.1219 ¶¶32, 35, 39.<sup>11</sup> But this evidence concerns Petitioner’s *prima facie* case; it should have been presented earlier. Consolidated Trial Practice Guide (“CTPG”) §II.I.

Dr. Simpson’s testing, old and new, directly conflicts with Huang2. Resp. 20-28 (multiple conflicts). For one, he depicts two minor peaks at 0°/180°, shown below, that are wholly absent from Huang2. *Id.*



Ex.1003 ¶125; Ex.1219 ¶¶32, 35, 39. Petitioner downplays these differences,

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<sup>11</sup> Whether masks are consistent with Ayres-2008 is irrelevant. Ex.1219 ¶38.

Dr. Simpson claimed to follow Huang2. Ex.1003 ¶125.

arguing these peaks “correspond to ‘background noise’” and are “perfectly consistent” with Huang2.<sup>12</sup> But Dr. Simpson tested Huang2’s Figure 1B, which Petitioner states Huang2 also tested. Pet. 36; Ex.1005, 1794. Any “background noise” in Figure 1B would also appear in Huang2’s FFT plot, but it does not. Ex.1220, 139:1-4; Ex.1005, Fig.1C. Petitioner’s explanation does not resolve the conflict.

Petitioner alternately characterizes Huang2’s FFT plot as depicting an average, but that explanation also fails. Huang2 does not state that its FFT plot reflects an average, nor did the Petition. Ex.1220, 100:16-101:14. Moreover, any background noise from Figure 1B would necessarily be reflected in an average plot to some extent; this is how averages work. Instead, Huang2 presents a perfectly bell-shaped plot without any minor peaks.

The Board should disregard evidence that conflicts with the reference upon which this ground relies. *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.”).

**b) It is scientifically invalid**

Dr. Simpson’s testing is scientifically unsound, non-reproducible, and entitled

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<sup>12</sup> Per §II.A.2.b, if the 0°/180° peaks are noise, they are excluded from the average.

to no weight. Dr. Mikos' criticisms are not quibbling over "certain details." Reply 11. He identified numerous deficiencies and unknown parameters that Dr. Simpson established as critical and that alter FFT analyses. Resp. 28-31; Ex.2015 ¶¶88, 93, 95; Ex.1220, 107:14-25 ("not scientifically rigorous and reproducible"), 118:18-23 ("[H]e didn't follow the guidelines that he himself stated in his own paper.").

Petitioner misses the mark arguing that Patent Owner cannot require "more detail in the prior art than appears in the challenged patent." Reply 11. These details do appear in the challenged patent: incorporated Ayres-2008 establishes the importance of the very parameters Petitioner now characterizes as insignificant "details." Ex.1010, 606-615; Resp. 28-31. It strains credulity for Dr. Simpson to disregard parameters he himself identified and which are incorporated by reference.

Moreover, Petitioner's cited cases do not excuse Dr. Simpson's insufficient description of his testing. Ex.1003 ¶125 ("I conducted my own analysis ... [as] described in Huang2 and the '227 patent."); Ex.1220, 116:17-24 (Q: "[D]idn't Dr. Simpson ... say that he followed the procedures set forth in Ayres?"; A: "The procedures to do what? I mean, to do the selection -- the circular selection? How to do the image analysis? To vary the illumination? It's not clear."). 37 C.F.R. §42.65(b) applies to Dr. Simpson even if he invented the Ayres-2008 method." Reply 11. Like every other expert before the Board, Dr. Simpson must demonstrate

“[h]ow the test was performed and the data was generated.” He did not.

**4. Huang2/Kuo do not render obvious tendon/ligament/nerve treatment**

**a) Petitioner’s new theories are untimely**

**(1) Kuo’s method**

The Reply presents a new theory that treats Kuo as a primary reference. Reply 14-17. Petitioner now argues a POSITA “would have been motivated to take the electrospun flat scaffold made by the techniques of Huang2, seed it with the desired cells, and roll it to treat a tendon or ligament,” per Kuo. *Id.* 17. But the Petition never proposed using Huang2’s scaffold in Kuo’s method, e.g., rolling Huang2. *Compare* Pet. 28-30, 39-41, *with* Reply 14-17. The Board recognized this:

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

DI 33-34. Indeed, Dr. Simpson did not realize the (alleged) “strong[] connection between Huang 2 and Kuo” until after filing his declaration. Ex.2017, 23:4-11 (“[T]here’s a much stronger connection ... than I realized at the time this document was finished.”).

Petitioner cannot put forth one theory in the Petition and then, after considering Patent Owner’s well-taken arguments and the Board’s preliminary conclusions, develop a new theory for Reply, without opportunity for meaningful

response.<sup>13</sup> *smaXtec Inc. v. ST Reproductive Techs., LLC*, IPR2024-01067, Paper 33 (PTAB Jan. 16, 2026) (declining to consider Reply that “presents a new position that Harvey is the primary reference to be modified with Risky[.]”); *Pioneer Pet Prods., LLC v. Oil-Dri Corp.*, IPR2022-01138, Paper 36 (PTAB Dec. 19, 2023) (declining to consider Reply with “additional reasoning and reliance on new expert testimony, coupled with new specifics as to the manner in which the references would be combined”); *Wasica Fin. GmbH v. Cont’l Auto. Sys.*, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (“Shifting arguments ... is foreclosed.”).

## **(2) Huang2’s fibroblasts**

The Reply also presents a new theory regarding cell seeding but then backtracks. Petitioner argues a POSITA would seed Huang2’s scaffold with “any cells ... to which the construct is intended to correspond.” Reply 16. This was not alleged in the Petition. Pet. 28-30, 39-41 (not altering Huang2’s cell-seeding). But the Reply then backtracks, arguing that Huang2’s original “fibroblasts” permit tendon/ligament repair after all. Reply 17-18; Exs.1204-1207. This should have

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<sup>13</sup> Paper 27 (noting that authorization to submit a motion to strike or new evidence was denied).

been addressed in the Petition. CTPG §II.I.<sup>14</sup>

**b) These belated theories fail**

**(1) Kuo's method**

These new theories are unsound. First, Kuo already takes an aligned scaffold, seeds it, rolls it, and treats tendon/ligament/nerve with it. Ex.1018 ¶5. Petitioner provides insufficient reasoning why a POSITA would have combined Huang2/Kuo to do what Kuo discloses.

Petitioner alleges that although Kuo “prefer[s]” aligned fibers, Kuo does not provide “testing evidence” of alignment, purportedly justifying Huang2’s inclusion. Reply 16; Ex.1219 ¶47. But this is belied by Kuo’s extensive disclosure of aligned fibers: “Described herein are methods and compositions using aligned nanofiber materials as scaffolds for engineering tendon or ligament tissues.” Ex.1018 ¶112; *id.* Fig.3B, ¶¶5, 9, 12, 21, 34, 48, 53, 79, 114-115.

The Board recognized this:

We note, however, that Kuo already discloses aligned fibers but further discloses the rolled structure to mimic the fascicles of muscle, tendon, nerve, or ligament tissue. It is not clear why a POSITA would have

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<sup>14</sup> Petitioner alleges this responds to the argument that Huang2 is designed for skin repair. Paper 28, 3-4. But Petitioner agrees Huang2 is designed for skin repair. Pet. 20. Had Petitioner intended to argue that Huang2’s seeded cells be modified to repair other tissues, that belonged in the Petition.

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.

DI 33. This preliminary finding was correct.

Petitioner also ignores the many reasons to avoid rolling Huang2's scaffold. Specifically, rolling limits diffusion into the scaffold, leading to cell death. Ex.2015 ¶122; Ex.2023, 145. And Dr. Simpson explained that rolling creates “‘seams’ ... resulting in discontinuities and possible weak connective points,” which risk “infiltration by unwanted interstitial fibroblasts and[/]or inflammatory cells.” Ex.2022, 3:54-4:8, 31:66-32:3. Rolled scaffolds also cause axons to “cluster and grow as a jumbled disorganized mass,” leading to “reduced axon targeting.” *Id.* 5:39-46. Dr. Simpson does not dispute this. Ex.1219 ¶¶50, 80.

Finally, Petitioner fails to demonstrate that Huang2's scaffold would have been capable of rolling without failure. As Dr. Mikos explained, the mechanical properties of Huang2's scaffold differ substantially from tendon/ligament/nerve tissue and from scaffolds—like Kuo's—designed to repair them. Ex.2015 ¶¶125-133.

## **(2) Huang2's fibroblasts**

Even if “differentiation of fibroblasts to myofibroblasts” is an essential healing pathway, Reply 18, Huang2 did not seed “fibroblasts.” Huang2 utilized specifically targeted cells: “normal human dermal fibroblasts” (“NHDF”) derived

from “newborn foreskin (R2F)”. Ex.1005, 1791-1792. These NHDFs are not synonymous with “fibroblasts.” Ex.1220, 175:23-176:13 (“Specific type of fibroblast was used in Huang2.... [N]ormal primary human skin fibroblast from newborn ... foreskin .... It’s a different type of fibroblast.”).

Petitioner’s evidence confirms fibroblasts “are not one unified cell population”; different subpopulations “have distinctly different effects on wound healing.” Ex.1204, 5. Accordingly, any tissue-repair success attributable to one fibroblast type cannot be attributed to another because of the heterogeneity between subpopulations. *Id.*

Petitioner’s evidence shows only that other fibroblasts—not Huang2’s NHDFs—were used for tendon/ligament repair. For example, Exhibit 1204 explains that “fibroblasts, which contribute to tendon healing, are located in the synovium and sheath of the tendon”; those tendon-derived cells are not NHDFs. Ex.1204, 5; Ex.1018 ¶16 (tenocytes); Ex.1205, 775-776 (non-human (pig)), 787 (endogenous host fibroblasts, e.g., from tendon, facilitated repair); Ex.1206, 2-3 (adult); Ex.1207, 894 (non-human (goat)), 901 (ligament repair only “to a lesser extent”).

These teachings do not apply to Huang2’s NHDFs. A POSITA would not have expected success in repairing tendon/ligament/nerve with Huang2’s NHDF-seeded scaffold. Ex.2015 ¶¶135-142 (“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.”).

**c) Huang2’s scaffold is inapplicable to these tissues**

If Kuo’s method were applied with Huang2’s scaffold, it would remain inapplicable to tendon/ligament/nerve repair because structural characteristics like elastic modulus, stiffness, and degradation rate differ from that required for those tissues. Ex.2015 ¶¶138-142; Resp. 35-39. For example, tendon/ligament repair requires 73.5 and 49.78 times more stiffness, and nerve repair requires 472 times less stiffness, than Huang2’s scaffold imparts. Ex.2015 ¶133. Additionally, degradation rate must be controlled to match the rate of new tissue formation, which varies among these tissues. *Id.* ¶¶139-140. Modifying these characteristics “would not have been obvious .... [It] requires tailoring of factors that are not accounted for in the Petition.” *Id.* ¶142.

Dr. Simpson alleges a POSITA could have optimized these characteristics to treat tendon/ligament/nerve. Reply 19. But the Petition did not propose modifying Huang2’s scaffold structure to do so. The Petition did not even acknowledge these structural differences, which are dispositive to success, let alone propose their modification.<sup>15</sup> Petitioner cannot propose new modifications for the first time on

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<sup>15</sup> The Reply incorrectly states the “modulus argument is based on the false

Reply. *Wirtgen Am., Inc. v. Caterpillar Inc.*, IPR2022-01397, Paper 27, 65 (PTAB Mar. 12, 2024) (improperly proposing a “newly asserted modification”).

**5. Huang2 does not disclose claims 2-6**

**a) Claims 2-3**

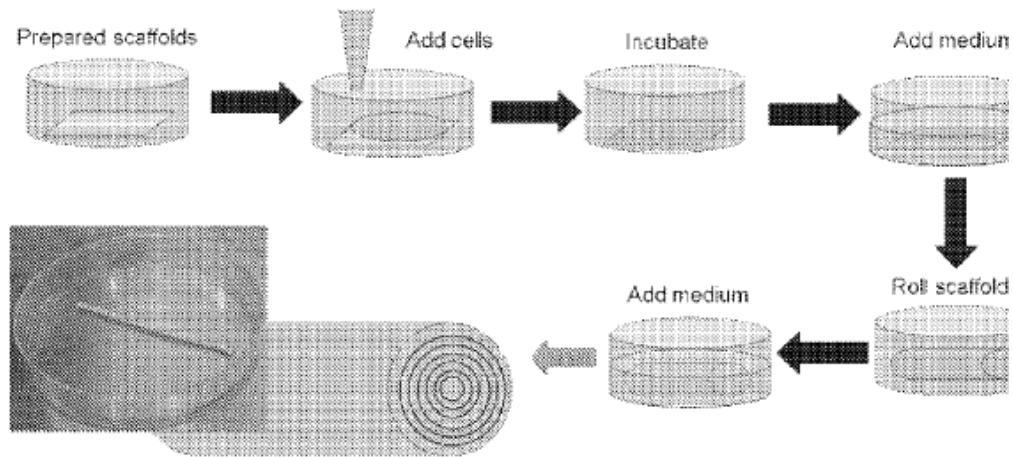
Claim 1 recites a method involving, e.g., “implanting at the tissue defect a scaffold ....”; claims 2-3 further limit “the scaffold” to “the form of one or more elongated sheets” or “a composite of multiple layers of one or more sheets.” Ex.1001, 23:29-41, 8:44-46 (“[A]n elongated sheet or a composite of multiple layers of sheets may be used to facilitate neuronal cell growth.”). Accordingly, the claims dictate the form of the scaffold when it is implanted per claim 1. The “comprising” transitional phrase does not alter the express claim requirements regarding form. *Id.*

Contrary to Petitioner’s argument, rolling a scaffold dictates that, when implanted, it is no longer in the form of one or more sheets. Reply 21; Ex.1018, claim 27 (implanting rolled scaffold). This is apparent from Kuo’s Figure 1, below, showing the difference between a scaffold, at the initial step, and a rolled scaffold

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assumption that a [POSITA] ... would use only dermal fibroblasts to treat a tendon injury.” Reply 19. Elastic modulus is a measurement of scaffold stiffness and must match the target tissue. Ex.2015 ¶¶125-133. Although cell-seeding must also match the target tissue, it is a separate issue.

ready for implantation, at the end.



Ex.1018, Fig.1.

**b) Claim 4-6**

*See supra* §II.B.4. Additionally, the Reply does not substantively address nerve repair. Reply 14-21.

**C. Belated attempts to rewrite the Petition fail to demonstrate unpatentability by Lee**

**1. Lee does not disclose the “result of a [FFT] analysis”**

**a) The Petition fails 35 U.S.C. §312(a)(3)**

It is Petitioner’s obligation to particularly identify its challenge. 35 U.S.C. §312(a)(3). Petitioner, therefore, must have alleged “with particularity” that Lee expressly disclosed the FFT analysis result and/or does so inherently. The Petition alleged neither.

The Board preliminarily recognized this. DI 36 (“Petitioner does not clearly assert in the Petition that the fibers taught by Lee necessarily or inherently satisfy

the FFT analysis result. Petitioner’s grounds based on Lee may ultimately fail on the merits due to this lack of specificity.”). Petitioner now attempts to recharacterize the Petition to cure this defect. Reply 22-24. First, Petitioner argues it stated that “Lee by itself also discloses” this element “by describing aligned PCL/collagen fibers,” where a POSITA “would have known and understood that Lee’s highly aligned fibers have the necessary FFT peaks.” *Id.* Second, Petitioner relies on the Petition’s statement that FFT “could be performed” and, if so, it “would show” alignment.<sup>16</sup> *Id.* 24; Pet. 50.

But this does not move the needle. As the Reply confirms, the Petition addressed only “aligned” fibers. These contentions are inapposite because claim 1 does not recite “aligned” fibers. Instead, it requires “a result of a [FFT] analysis ... hav[ing] major adjacent peaks that are about 180° apart from each other.” The Petition does not particularly contend that Lee expressly discloses this FFT analysis result, nor does the Petition “clearly assert ... that the fibers taught by Lee necessarily or inherently satisfy the FFT analysis result.” DI 36. Put simply, contending that Lee shows “aligned PCL/collagen fibers,” or that an undisclosed FFT analysis “could be performed” or “would show the fibers were oriented ... in

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<sup>16</sup> Petitioner improperly attempts to incorporate Dr. Simpson’s statements, mentioned nowhere in the Petition. Reply 24; 37 C.F.R. §42.6(a)(3).

an aligned manner,” is not a contention regarding the claimed FFT analysis result.

Petitioner’s argument that aligned fibers, “by definition, must have two major peaks in the FFT 180° from each other” is wrong. Reply 22-23; §II.A. First, Petitioner fails to define “aligned” fibers with any precision. Second, Ayres-2008’s statement that “aligned elements exhibit ... two larger peaks” does not speak to the defined claim language. §II.A. The claimed “major adjacent peaks” require a height higher than the average, which indicate a primary axis of alignment, while minor peaks necessarily present in the FFT result indicate a secondary/additional axis of alignment. *Id.* This is not simply a long-winded way of claiming “aligned fibers”; it requires more.

**b) Dr. Simpson’s testing is insufficient**

As discussed above, §II.B.3.b, Dr. Simpson’s testing is invalid and non-reproducible. His current opinion that even “a considerable amount of noise does not alter the presence of two alignment peaks” is belied by earlier statements. Ex.1219 ¶74; Ex.1010, 605. In fact, Dr. Simpson previously explained that images “composed largely of optical noise,” like Lee, are “unsuitable for [FFT] analysis” because “individual fibers are not detected.” Ex.1010, 605; Ex.1013, 7 (Dr. Simpson stating “noise can degrade the absolute alignment value assigned to a scaffold by FFT analysis”). His contradictory statements now should not be credited, especially where Lee’s “individual fibers are not detected” in the tested image. Resp. 49-52

(reproducing a portion of Lee’s image, shown below).



## **2. Petitioner’s new obviousness arguments fail**

Petitioner is incorrect in its belated argument—absent from the Petition—that “if a POSA ... wanted to confirm fiber alignment” they would do so with FFT because it is “non-destructive.” Reply 25; *Innoscence Tech. Co., Ltd. v. Efficient Power Conversion Corp.*, IPR2023-01383, Paper 39, 43 (PTAB Mar. 18, 2025) (declining to consider Reply providing “new reasons that ... a POSITA would have used [a reference’s] process”).

Both experts acknowledge SEM is destructive. Ex.2017, 73; Ex.1220, 53:21-54:10. But Lee already created SEM images for use in determining alignment. Ex.1011 ¶65. Neither Petitioner nor Lee provide any reason why a POSITA would create a second set of images—brightfield images—for non-destructive FFT testing when SEM images already exist upon which FFT testing could have been performed (but was not). Resp. 45-49.

## **3. Lee/Kuo do not render obvious tendon/ligament/nerve treatment**

Although the Board preliminarily found that common treatment of muscle in Lee and Kuo portended success in treating other tissues, DI 40, that initial finding has been rebutted. Dr. Mikos explained dispositive differences between muscle, in

Lee, and tendon/ligament/nerve. Ex.2015 ¶¶175-199 (different vascularization, elastic moduli, cell-seeding, degradation rate). These differences dictate that Lee’s scaffold would not successfully repair these tissues.

**a) Muscle is highly vascularized**

Dr. Mikos testifies that muscle regenerates rapidly “due to its high vascularity and abundance of stem cells.” Ex.2015 ¶192. Tendon/ligament/nerve, by contrast, have lower vascularity and consequently regenerate more slowly. *Id.* ¶¶192, 196 (“The low vascularity of tendon, ligament, and nerve tissue affects their regenerative capacity.”). Petitioner’s Reply evidence confirms this testimony: “tendon is a relatively avascular tissue and has a low cell density, leading to a decreased regeneration potential.” Ex.1204, 1.

Petitioner and Dr. Simpson fail to even address this dispositive difference in vascularity. The undisputed record confirms that 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 muscle tissue (which Lee’s scaffold is designed to repair) as compared to that of tendon, ligament, or nerve tissue.” Ex.2015 ¶196.

**b) Petitioner’s belated theory fails**

As with Huang<sup>2</sup>, Petitioner now contends that a POSITA would have performed Kuo’s method with Lee’s scaffold. Reply 26; Ex.1219 ¶¶78-80. This

belated theory is improper.

This theory is also unsound for reasons like those above. Namely, Kuo already takes an aligned scaffold, seeds it, rolls it, and treats tendon/ligament/nerve with it. Ex.1018 ¶112; DI 33. Petitioner presents insufficient reasoning why a POSITA would introduce Lee to achieve what Kuo already discloses. Petitioner also ignores very real reasons to avoid rolling Lee's scaffold, discussed above. Ex.2022, 3:54-4:8 (infiltration), 5:39-46 (reduced axonal targeting); Ex.2015 ¶122 (cell death); DI 40 (“[T]here may be some differences in the specific structures of the scaffolds, such as the rolled structure disclosed in Kuo that is not disclosed in Lee.”).

#### **4. Lee's scaffold is inapplicable to these tissues**

The Reply alleges a POSITA could optimize structural features of Lee's scaffold to facilitate tendon/ligament/nerve repair. Reply 26. But, as with Huang2, the Petition did not allege that a POSITA would have, or could have, modified structural characteristics of Lee's scaffold, such as elastic modulus or degradation rate, to ensure success. The Petition did not even acknowledge these structural differences, let alone propose their modification.

Dr. Mikos establishes that success would not have been expected. Ex.2015 ¶¶183-199. For example, Lee's elastic modulus is exceedingly low, much too low to repair tendon/ligament/nerve, which require moduli over 687,500/465,625/19-times higher. *Id.* ¶188. Although Petitioner does not dispute these substantial

differences in structural features, Petitioner nonetheless sweeps aside the massive modifications needed to address them. But Petitioner's own evidence disproves the ease with which these modifications could have been achieved, had they been proposed in the Petition. Ex.1011 ¶¶50 (synthetic polymers impact rigidity and degradation; natural polymers impact biocompatibility), 51 (surface characteristics impact cell adhesion/proliferation), 52-53 (varying ratios of synthetic/natural polymers to control characteristics); Ex.1209, 1198 ("The effects of the solution properties can be difficult to isolate since varying one parameter can generally affect other solution properties." ).<sup>17</sup>

**5. Claims 2-6 are not obvious**

**a) Claims 2-3**

Rolling a scaffold dictates that the scaffold, when implanted per claim 1, is no longer in the form of a sheet or multiple layers of a sheet. Ex.1018, claim 27 (implanting rolled scaffold), Fig.1.

**b) Claim 4-6**

*See supra* §II.C.3. Additionally, the Reply does not substantively address nerve repair. Reply 22-27.

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<sup>17</sup> The Reply fails to address Dr. Mikos' testimony that Lee's muscle cells (hSkMCs) are incapable of differentiation into tendon/ligament/nerve. Ex.2015 ¶¶190-191.

### III. CONCLUSION

Petitioner failed to meet its burden to demonstrate unpatentability; that burden never shifted to Patent Owner.

Dated: March 25, 2026

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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 5580 words as counted by Microsoft Word, the word-processing system used to prepare this preliminary response.

Dated: March 25, 2026

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### **Certification of Service**

Pursuant to 37 C.F.R. §42.6, the undersigned certifies that on March 25, 2026, 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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