

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

LIFENET HEALTH,
Patent Owner.

IPR2025-00248
U.S. Patent No. 10,137,223

PATENT OWNER'S SUR-REPLY

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TABLE OF EXHIBITS

Exhibit Number	Description
2001	Intentionally Left Blank
2002	Intentionally Left Blank
2003	Intentionally Left Blank
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”)

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 a specific FFT analysis result having adjacent "major peaks," which are expressly defined. It recites:

1. A scaffold comprising one or more electrospun fibers comprising collagen, wherein a fast Fourier transform (FFT) analysis result of the fibers have adjacent major peaks with about 180° apart from each other.

Ex.1001, 23:6-9.

The Petition's grounds fail for four reasons. First, Huang² lacks the claimed FFT analysis result having "major peaks," under the Specification's lexicographic definition and Petitioner's proposed construction. Second, Lee does not disclose FFT analysis results at all, and the Petition fails to demonstrate inherency. Third, Petitioner propounds unreliable expert testing and improper new Reply theories. And fourth, dependent claims 2-4 and 12 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 FFT result where "the shape of its peaks indicat[e] the extent of alignment." *Id.* 9. 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 ¶¶57-58; Ex.1010, 610 (“A high and narrow peak indicates a more uniform degree of fiber alignment, a broad peak, or a shoulder on the peak indicates that more than one axis of alignment may be present.”).

The ’223 patent claims its electrospun scaffold very specifically. It did not recite “aligned fibers,” a term Petitioner and its expert fail to define with any precision. Indeed, Dr. Simpson previously characterized fibers as “aligned” even though he acknowledged they were not. Ex.1212, 116 (“While results would indicate that *truly aligned fibers were not created*, scaffolds created with a high mandrel rotational speed were *referred to as aligned scaffolds for the sake of simplicity* in reporting results.”).¹

Instead, the ’223 patent claims a specific FFT result having “adjacent major peaks with about 180° apart from each other.” Ex.1001, 23:6-9. The Specification expressly defined those “major peaks.” 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

¹ Unless noted, emphasis added/internal citations omitted.

“calculat[ing] an arithmetic mean” is undescribed. Reply 4-6; Ex.1001, 13:3-7.

This fails. Petitioner defines a POSITA as a two-year Ph.D. student who understands mathematical FFT analysis. Pet. 18-19. 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. 12 (“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. 19 (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:

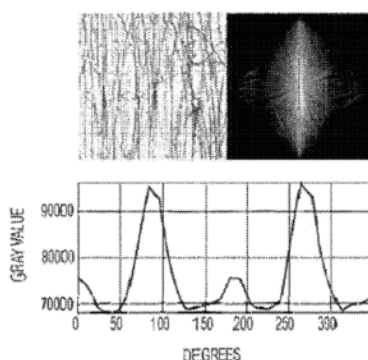


FIG. 8A

Ex.2015 ¶56 (90°/270° peaks higher than average height).

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

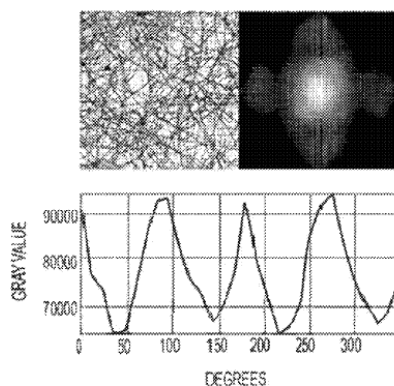


FIG. 8B

Ayres-2008, incorporated by reference, likewise explains, “peaks of nearly uniform height”—like Figure 8B—indicate a random scaffold. 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 8-9. Not so.

First, the Specification is silent regarding peak height and Dr. Mikos testifies that 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 apart from measurement/reporting error. Ex.1219 ¶19.² This contrasts with Figure 8A, where the 90°/270° peaks plainly exceed the average, even accepting some “guesstimat[ion]” or measurement error. Ex.2015 ¶56 (“approximat[ing]” heights; exceeding average by 10,000); Ex.1220, 63:16-18.

Second, Dr. Mikos testifies that in a FFT plot “what appears at 0 degrees would appear at 360 degrees”; it is “the same peak.” Ex.1220, 62:17-20. But Figure 8B is “cut at 350^[o]”; one “cannot clearly see where it goes” or “where it ends at ... 360 degrees.” *Id.* 66:18-22 (Dr. Mikos: “I wanted to see it at 360 degrees.”); Ex.1001, Fig.8B (discontinuous after 350°). Accordingly, the 0°/360° peak’s apex/height *is not depicted*; Dr. Simpson simply speculates regarding height (and the four-peak average). Ex.1220, 69:15-19 (Dr. Mikos stating, “[t]he peak at 0 degrees ... it’s 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 in the patent*. It is perfectly reasonable to incorporate Ayres-2008 for background knowledge while claiming a

² These minor deviations must be statistically *insignificant* to align with his testimony that FFT peaks “*repeat* between 0°-180° and 180°-360°.” Ex.1003 ¶46.

specifically defined embodiment.

b) Prosecution history

Petitioner improperly relies upon the applicant's *silence* during prosecution. Reply 9-10. 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 ¶¶57-58.³ 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 '223 patentee acted as lexicographer and may "use terms in a manner other than their

³ Petitioner misrepresents Dr. Mikos experience. Reply 11-12. 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.

ordinary meaning, as long as the special definition of the term is clearly stated in the patent specification or file history,” as it is here. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1378 (Fed. Cir. 2005) (“[A]pplicant ... may define ‘black’ as ‘white.’”).⁴

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 8; Ex.2015 ¶58. This reflects real-world scaffolds where “high frequency signals” that “reflect fiber alignment” are plotted as “prominent or ‘major’ peaks,” and where “fibers that present additional orientations” are plotted as “smaller or minor peaks.” Ex.2015 ¶¶57-58; Ex.1001, Fig.8A (depicting primary and additional orientations).⁵

⁴ There is no inconsistency with Patent Owner’s district court pleadings. Reply 10-11. Petitioner points to the Complaint, which quotes Petitioner’s product description. Ex.2005 ¶¶49-52. Neither infringement nor claim construction positions have been exchanged.

⁵ This real-world scaffold contrasts with Ayres-2008’s perfectly aligned spaghetti. Ex.1010, 606, 614.

b) Noise is not a “peak”

Petitioner wrongly argues this definition “limits the claims to FFT plots that contain noise or imperfections.” Reply 8. Not so.

FFT peaks reflect alignment. Ex.2015 ¶¶57-58; Ex.1010, 610. Figure 8A’s FFT result depicts primary fiber alignment with major peaks and secondary alignment with minor peaks.

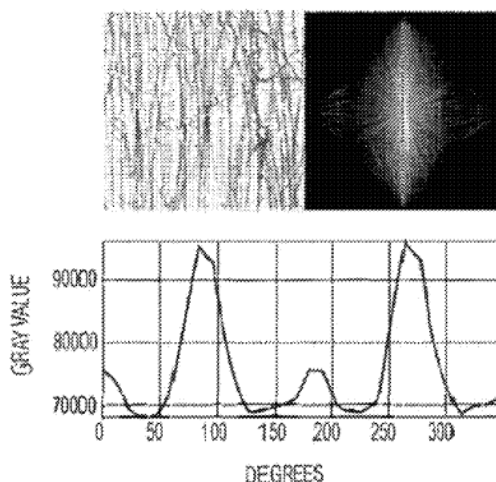


FIG. 8A

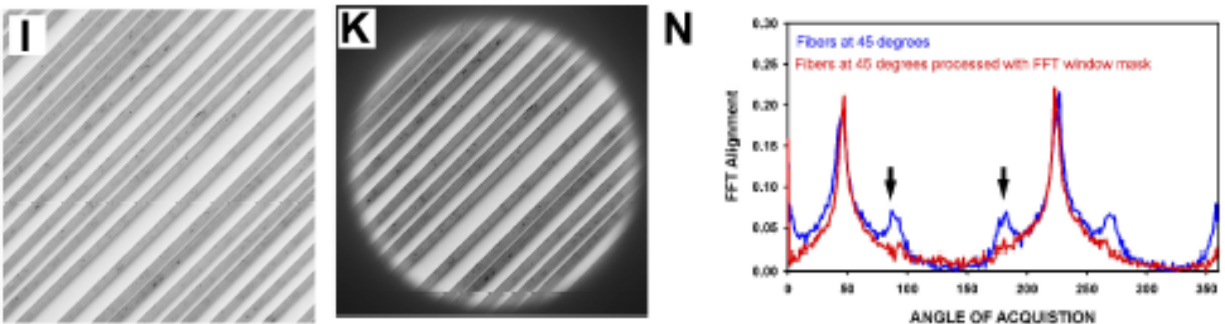
Figure 8A’s SEM image confirms this. Ex.1220, 77:14-78:24 (Dr. Mikos explaining the 0°/180° peaks “represent a secondary axis of alignment ... especially when I see the top left [SEM] image”).

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/resolution 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 (“jumping up and down”), 115:23 (“very small”). 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 (“[M]inor peaks correspond to ... a secondary axis of alignment. I would not classify them ... as noise.”), 78:7-11 (similar); 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 7-8; Ex.1010, Fig.3. 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” (Figure 3I)

creates edge effect artifacts that add “spurious information” to the FFT (arrows). *Id.* 613, 615. Because this “spurious information” can be removed by masking (Figure 3K), Petitioner argues the “same scaffold would fall outside the claims when plotted with a mask that removes noise (red trace) but fall within them when plotted without a mask (blue trace).” Reply 7-8.

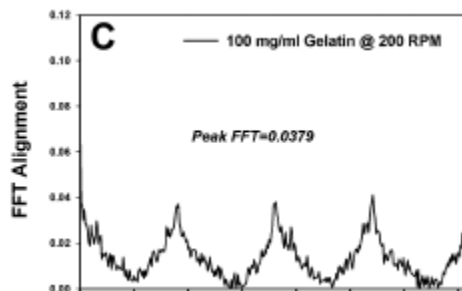
This is incorrect; neither trace falls within the claims because neither has “major peaks.” Ex.1010, 613-614. The “spurious information” (arrows) does not reflect fiber alignment; Dr. Simpson explains these artifacts are caused by the fibers’ position relative to the image border. *Id.* 613.⁶ They are not “peaks” included in the average peak height.

⁶ 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.’”⁷ Reply 6. But a FFT result with peaks of identical height also lacks “major peaks” under Petitioner’s construction because a “qualitative,” “visual assessment of the relative sizes of the peaks” demonstrates they are identical; neither is “major” when visually assessed relative to the other.

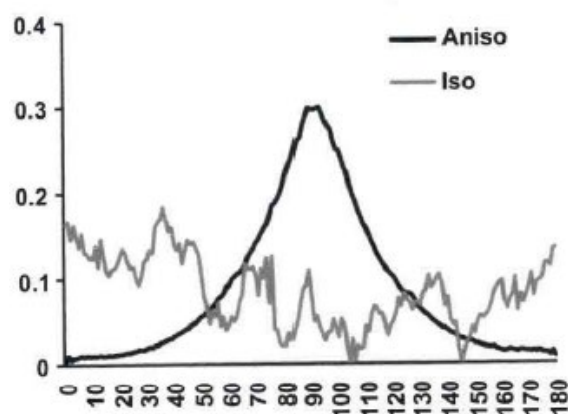
Dr. Simpson similarly testifies that, in the FFT result below, he “would not refer to that [peak at 90°] as a major peak because all the peaks in that particular plot look like they’re essentially very similar in height.”



Ex.2017, 88:7-15.

⁷ Ayres-2008 does not qualitatively identify peaks; it quantifies “alignment value ... by visually inspecting and selecting the maximal value from the peak.” Ex.1010, 613.

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



Ex.1005, Fig.1C. Assuming *arguendo* that an 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. Cf. Ex.2017, 88:7-15 (“[A]ll the peaks ... look like they’re essentially very similar in height.”).

B. Huang2 does not anticipate

1. No “major peaks”

Huang2’s FFT result, above, lacks “major peaks.” 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 ¶¶66-67; 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.

2. Dr. Simpson fails to prove anticipation

a) His testing conflicts with Huang2

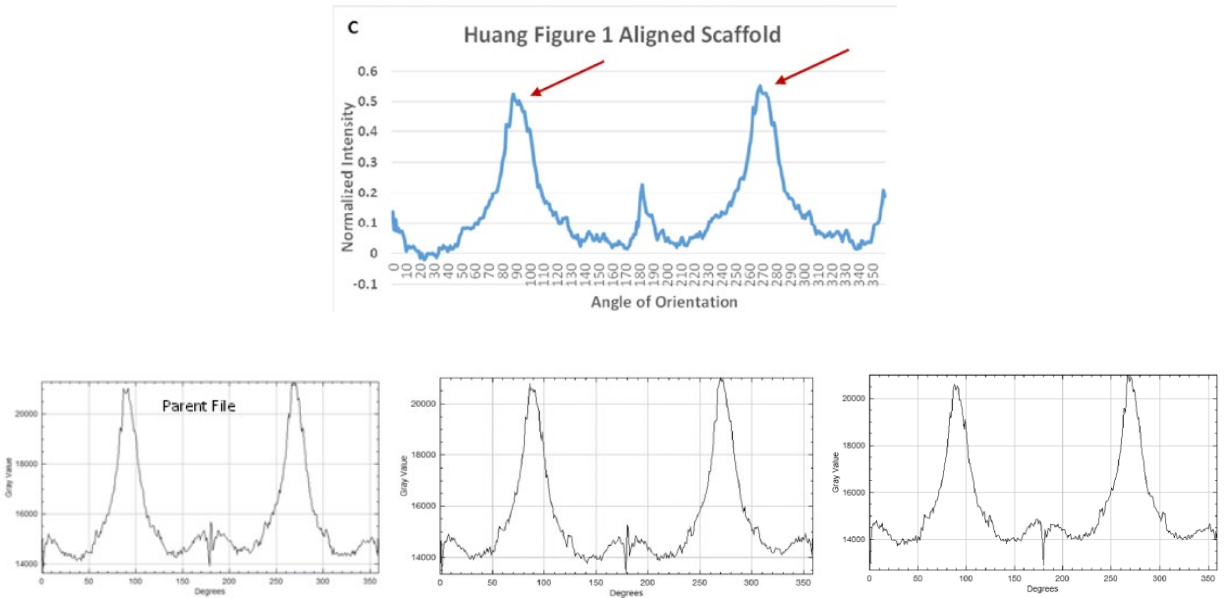
To support anticipation, Petitioner relies upon FFT testing performed by Dr. Simpson. As discussed in the Response, Dr. Simpson originally performed a *different* analysis than Huang2 (among other deficiencies). Resp. 16-26. Dr. Simpson misunderstood Huang2's disclosure and mistakenly applied a mask 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, 39.⁸ But this evidence concerns Petitioner's *prima facie* case; it should have been presented earlier.⁹ Consolidated Trial Practice Guide ("CTPG") §II.I.

Dr. Simpson's testing, old and new, *directly conflicts* with Huang2. Resp. 14-26 (additional conflicts). For one, he depicts two minor peaks at 0°/180°, shown below, that are *wholly absent* from Huang2. *Id.* 23-26.

⁸ Whether masks are consistent with Ayres-2008 is irrelevant. Ex.1219 ¶38. Dr. Simpson claimed to follow *Huang2*. Ex.1003 ¶110.

⁹ See Paper 28 (noting that authorization to submit a motion to strike or new evidence was denied).



Ex.1003 ¶110; Ex.1219 ¶¶32, 35, 39. Petitioner downplays these differences, arguing these peaks “correspond to ‘background noise’” and are “perfectly consistent” with Huang2.¹⁰ But Dr. Simpson tested Huang2’s Figure 1B, which Petitioner states Huang2 also tested. Pet. 30 (“Huang2 graphed its FFT analysis of the aligned (anisotropic) *fibers photographed in Figure 1B* in Figure 1C.”); 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

¹⁰ Per §II.A.2.b, if the 0°/180° peaks are noise, they are excluded from the average.

reflects an average, nor did the Petition. Pet. 30; Ex.1220, 100:16-101:14. Moreover, any background noise from Figure 1B necessarily would be reflected in an average plot to some extent; this is how averages work. Instead, Huang2 presents a perfectly bell-shaped plot without any indication of minor peaks.

The Board should disregard evidence that conflicts with the reference upon which this anticipation 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) His testing is scientifically invalid

Dr. Simpson’s testing is scientifically unsound, non-reproducible, and entitled to no weight. Dr. Mikos’ criticisms are not “quibbling over minor details.” Reply 13. He identified numerous deficiencies and unknown parameters that alter FFT analyses and that Dr. Simpson himself established as critical. Resp. 16-29; Ex.2015 ¶¶78 (“These artifacts adversely affect plot shape.”), 83 (“[This] testing would produce inaccurate results.”), 85 (“[T]he circular selection ... can affect the outcome of the analysis including changes in the shape of alignment peaks.”); Ex.1220, 107:14-25 (“[T]his figure was produced under conditions which are 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 13-14. First, these details do appear in the challenged patent: incorporated Ayres-2008 establishes the importance of the very parameters Petitioner characterizes as “minor details.” Ex.1010, 606-615; Resp. 16-29. It strains credulity for Dr. Simpson to disregard parameters he himself identified and which are incorporated by reference.

Second, Petitioner’s cited cases concern obviousness. They do not support an argument that Huang2 anticipates based on Dr. Simpson’s insufficiently described testing. Ex.1003 ¶110 (“I conducted my own analysis ... described in Huang2 and the ’223 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 is invented the Ayres-2008 method. Reply 13. 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.

3. Huang2 does not disclose claims 2-4

Petitioner’s anticipation case against dependent claims 2-4 fails on their own merits, regardless of claim 1. Although Huang2 is silent regarding these claim limitations, Petitioner chose to present an anticipation case nonetheless, leaving inherency as the only plausible allegation. But inherency requires strict proof, which

is lacking here.

“The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (“probabilities or possibilities” insufficient). Inherency “is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation.” *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002). “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).

a) Claim 2

Claim 1 recites a “scaffold comprising one or more electrospun fibers”; claim 2 further limits “the fibers” to “type I collagen in its native triple helical structure.” Ex.1001, 23:6-11. Accordingly, the collagen must be in native triple-helical form after being “electrospun” into “the fibers.” *Contra* Reply 17.

Huang2 is silent regarding its electrospun fibers’ structure. And the record confirms Huang2’s fibers are exposed to numerous denaturing materials known to destroy native triple-helical structure. Resp. 29-31 (PCL, HFIP). Petitioner’s speculation that native triple helical form may exist does not establish inherency.

For example, Petitioner does not dispute that Huang2 uses HFIP or that HFIP denatures collagen out of its native triple-helix. Reply 16-18; Ex.2015 ¶¶108-113.

This is well-known: “Electro-spinning collagen out of fluoroalcohols denatures collagen to gelatin.” Ex.2019, 2303, 2294 (“disrupted triple-helical” structure). Petitioner’s own evidence confirms as much: “electrospinning of biological materials [e.g., collagen] is less versatile because a suitable solvent that does not compromise its integrity has to be used.” Ex.1209, 1205.

Given these undisputed facts, Petitioner simply argues that other, different fibers maintained native triple-helical structure after dissolution in HFIP. Reply 16-18.¹¹ But that is irrelevant to Huang2’s fibers. As Dr. Mikos testifies, specific biomolecules in other fibers protected against denaturation. Ex.1220, 124:14-19, 127:17-128:1 (“other biomolecules” including “glycoproteins and proteoglycans ... helped preserve the bioactivity of collagen” in other fibers). Petitioner presents no evidence that Huang2’s fibers are similarly protected.

It is Petitioner’s burden to prove inherency, which “may not be established by probabilities or possibilities.” *PAR Pharm.*, 773 F.3d at 1195. Petitioner failed.

b) Claim 3

Petitioner also fails to demonstrate “less than about 8 wt % residual calcium”

¹¹ Ex.1209 is a review article. Petitioner failed to submit the underlying publications, so applicable differences cannot be examined. Ex.1209 should not be considered. Ex.1220, 138:1-7 (Dr. Mikos’ similar objection), 141:14-142:20.

in Huang2's fibers. Huang2 is silent regarding its residual calcium level. Petitioner's speculation that this level may be present is insufficient. Resp. 31-33.

Petitioner does not dispute that Huang2 uses fetal bovine serum ("FBS") or that FBS imparts calcium to electrospun fibers. Reply 18; Ex.2015 ¶¶117-120; Ex.1005, 1792. Instead, Petitioner argues that FBS is used for cell culture, which is not required by the claim. But Huang2's only disclosed embodiment—and that upon which Petitioner relies—cultures cells in FBS to study the cells' "phenotypic expressions" on different scaffolds. Ex.1005, 1791-1792. Accordingly, Petitioner fails to show that Huang2's scaffold, which includes cells cultured in FBS, necessarily contains less than 8 weight-percent residual calcium. Ex.2015 ¶119 (Dr. Mikos explaining fibers chelate calcium from FBS, especially where PCL is present, like in Huang2).

Petitioner complains this argument is "speculative." Not so. It is based on Huang2's express disclosure and is less speculative than Petitioner's contentions, based only on Huang2's silence. Pet. 34 (Huang2 "does not indicate any calcium was used" and "did not 'incorporate' or otherwise use calcium"). The burden is Petitioner's alone, and Petitioner failed.

c) Claim 4

The Reply does not dispute that Huang2 fails to disclose the 60-90% porosity of claim 4. Reply 16-18; Resp. 33-36; DI 28-29 (unlikely to prevail).

C. Improper reply arguments do not resuscitate Huang2/Kumbar

The Petition alleged that a POSITA would have implemented Kumbar's porosities in Huang2's scaffold to mimic skin extracellular matrix ("ECM"). Pet. 44-46. The Petition alleged a POSITA would have done so "using well-known methods including freeze-drying, salt leaching, and gas foaming." *Id.* 46-47. But, as explained in the Response, Kumbar's porosities are inapplicable to Huang2 because Kumbar discloses non-aligned, pure collagen scaffolds generated with "notably different electrospinning parameters." Resp. 36-39. "Because the electrospinning polymers differ, the electrospinning solution properties—and consequently the porosities—of Huang2 and Kumbar also necessarily differ." *Id.*

The Reply does not dispute this. Reply 18-19. Instead, Petitioner improperly raises a new theory: a POSITA would adjust electrospinning parameters to alter fiber diameter to reach the claimed porosity. *Compare* Pet. 44-47, *with* Reply 18-19. This is improper and insufficient.

1. Kumbar remains inapplicable

Huang2 and Kumbar electrospin fibers using different polymers: Huang2 with a 3:1 PCL/collagen blend and Kumbar with pure collagen. Ex.1005, 1792; Ex.1006, 8. A POSITA would not expect to achieve Kumbar's porosity in Huang2's scaffold because of their significantly different alignments and polymer solutions. Ex.2015 ¶133 ("[D]ifferent solution properties ... directly impact scaffold porosity.");

Ex.1006, 3 (“[P]orosity and pore-size distribution greatly depend on the[] parameters selected for electrospinning.”).

Petitioner’s new evidence is also drawn to different polymers. Ex.1211, 7 (PLGA); Ex.1212, 116 (fibrinogen); Ex.1213, 1207 (PLGA/gelatin). Dr. Mikos’ testimony applies equally: “the presence of PCL in Huang2’s PCL/collagen blend increases the solution viscosity ... [and] produces fibers with larger fiber diameter.” Ex.2015 ¶¶134-135. Petitioner fails to show that Exhibits 1211-1213, which also lack PCL/collagen, are any more applicable than Kumbar. A “POSITA would not have expected success in modifying Huang2’s scaffold” based on Kumbar or any of these new exhibits. *Id.* ¶168.

2. Adjusting electrospinning parameters is insufficient

Petitioner’s new theory also fails.¹² The Petition did not discuss adjusting electrospinning parameters or fiber diameters. Pet. 44-47. Instead, the Petition stated that porosity could be altered by different methods: “freeze-drying, salt leaching, and gas foaming.” *Id.* 46. Shifting to a new theory on Reply is improper:

[T]he expedited nature of IPRs bring with it an obligation for petitioners to make their case in their petition; ‘the Board is not permitted to entertain ‘[s]hifting arguments’ but must, instead, reject any ‘entirely new theory of *prima facie* obviousness absent from the petition.’

¹² It is unclear how Kumbar fits in this new theory at all.

Corephotonics, Ltd. v. Apple Inc., 84 F.4th 990, 1002 (Fed. Cir. 2023); *Pioneer Pet Prods., LLC v. Oil-Dri Corp.*, IPR2022-01138, Paper 36 (PTAB Dec. 19, 2023) (declining to consider Reply arguments, backed by new expert testimony and examples, which “goes far beyond the limited analysis in the Petition,” where “Petitioner provides no reason why it could not have been included in the Petition”).¹³

Regardless, Petitioner fails to establish that a POSITA would have modified Huang2 to reach the claimed porosity. Petitioner’s Reply addresses whether a POSITA could have modified electrospinning parameters. Reply 19 (“[A POSITA] would understand how to obtain such ranges.”). It does not sufficiently address why a POSITA would have done so. To the contrary, Petitioner’s alleged motivation—mimicking skin ECM—is already achieved by Huang2. Pet. 44-47; Ex.1005, 1791; *Edwards Lifesciences Corp. v. Aortic Innovations LLC*, IPR2023-01232, Paper 10

¹³ Petitioner alleges this responds to Patent Owner’s argument about different electrospinning parameters in Huang2/Kumbar. Paper 29, 3. But that well-taken argument does not permit Petitioner to propose new modifications on Reply. CTPG §II.I (“‘Respond’ ... does not mean proceed in a new direction with a new approach as compared to the positions taken in a prior filing.”).

at 36-37 (PTAB Feb. 7, 2024) (finding the purported motivation “inchoate” and “unpersuasive” because the “benefits” of the combination “are already conferred”); *Virtek Vision Int’l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 888 (Fed. Cir. 2024) (“A reason for combining must exist.”).

Petitioner also does not establish a reasonable expectation of success. First, Petitioner’s cited evidence demonstrates that adjusting electrospinning parameters is unpredictable: “The effects of the solution properties can be difficult to isolate since varying one parameter can generally affect other solution properties.” Ex.1209, 1198. Dr. Simpson agrees: “The only aspect of electrospinning that is not easy to directly control is the size of the scaffold’s pores.” Ex.1212, 116.

Second, Dr. Mikos explained that porosity turns on two factors: fiber density (dictated by alignment/packing) and fiber diameter (which dictates pore size). Ex.2015 ¶130; Ex.1214, 7 (“Porosity and pore size ... are mainly dependent on the fiber diameter and their packing density.”). But Petitioner and Dr. Simpson ignore fiber density altogether. Ex.1219 ¶54. Accordingly, even if a POSITA would have modified Huang2’s electrospinning parameters, Petitioner still does not account for the impact that fiber density would have on porosity.

Indeed, Petitioner relies upon Huang2 for its “highly aligned” fibers. Pet. 29. The record confirms that maintaining Huang2’s aligned morphology will result in lower porosity regardless of fiber diameter: “[R]andomly-oriented nanofibrous

scaffolds showed higher porosity than the aligned ones, probably due to the intertwined structure of the randomly-oriented” fibers. Ex.1213, 1207; Ex.1018 ¶112 (“a major limitation of aligned scaffolds” is “low porosity as a result of closely packed aligned fibers”); Ex.2015 ¶130 (“[T]ightly packed aligned fibers ... decreas[e] the structure’s porosity.”). Petitioner’s new theory fails.

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

1. Lee does not anticipate the “[FFT] analysis result”

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

The Board preliminarily recognized that the Petition violated 35 U.S.C. §312(a)(3):

Petitioner does not clearly assert in the Petition that the fibers taught by Lee necessarily or inherently satisfy the FFT analysis requirement. Rather, Petitioner only asserts that “it was well known at the time of filing that an FFT analysis *could be* performed to further confirm alignment,” and “[t]his *would show* the fibers were oriented on the scaffold in Lee in an aligned manner.” Petitioner’s grounds based on Lee may ultimately fail on the merits due to this lack of specificity.

DI 37-38.

Recognizing this, Petitioner attempts to rewrite the Petition to argue it asserted express and inherent anticipation. Reply 20-21. First, Petitioner contends it stated that “Lee discloses aligned PCL/collagen fibers that meet this [FFT result] element” because a POSITA “understood that Lee’s highly aligned fibers have the necessary FFT peaks.” *Id.* 20-21. Second, Petitioner relies on the Petition’s statement that

FFT “could be performed” and, if so, it “would show” alignment.¹⁴ *Id.* 22.

This does not move the needle. Petitioner was obliged to identify its challenge in the Petition. 35 U.S.C. §312(a)(3). The Petition, therefore, must have alleged “with particularity” that Lee expressly disclosed the claimed FFT analysis result and/or did so inherently. It alleged neither.

Instead, consistent with its attempt to rewrite the claims, the Petition argued only about “aligned” fibers. Pet. 52-53. This is inapposite because claim 1 does not recite “aligned” fibers; it requires a specific “[FFT] analysis result ... hav[ing] adjacent major peaks with about 180° apart from each other.” The Petition did not particularly contend that Lee expressly disclosed this result, nor did the Petition clearly assert inherency, as the Board recognized. DI 37. Put simply, arguing that “Lee discloses aligned PCL/collagen fibers,” or that FFT analysis “could be performed” or “would show the fibers were oriented ... in an aligned manner,” are not contentions regarding the claimed “FFT analysis result.” *Id.* 38; Resp. 41-43.

Petitioner is wrong in arguing that aligned fibers, “by definition, must have two major peaks in the FFT 180° from each other.” First, Petitioner’s descriptions

¹⁴ Petitioner cannot incorporate Dr. Simpson’s arguments, absent from the Petition. Reply 22.

of “aligned” fibers lack any precision. In fact, Dr. Simpson previously characterized fibers as “aligned” even though they were not. Ex.1212, 116 (acknowledging that “truly aligned fibers were not created” but nonetheless referring to scaffolds created with high mandrel speed as “aligned scaffolds for the sake of simplicity”). Clearly, “aligned” is not a definitional proxy for a specific FFT result having “major peaks” as claimed, when “aligned” may also refer to *non-aligned* fibers.

Second, Ayres-2008’s statement that “aligned elements exhibit ... two larger peaks” does not speak to the defined claim language. Reply 20. The claimed “major peaks” require a height higher than the average, which indicates a primary axis of alignment, while minor peaks necessarily present in the FFT result indicate a secondary/additional axis of alignment. This is not simply a long-winded way of reciting “aligned fibers”; it requires more.

b) Dr. Simpson’s testing is insufficient

As discussed above, Dr. Simpson’s testing is invalid and non-reproducible. Dr. Simpson fails to disclose testing aspects as critical as whether he applied a mask to Lee’s image. Resp. 47-51.

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 ¶63; Ex.1010, 605. In fact, Dr. Simpson previously explained that images “composed largely of optical noise,” like Lee (below), 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. 45-46 (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 ... 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 redundant, 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. 59-63.

3. Lee does not disclose claims 2-4 or 12

a) Claims 2-3

Lee is silent regarding its fibers' structure or residual calcium level. As above, it is undisputed that HFIP, used by Lee, degrades collagen. Ex.1011 ¶¶63; Ex.2019, 2294. And it is undisputed that FBS and glutaraldehyde, used by Lee, impart calcium to fibers. Ex.1011 ¶¶37, 63; Ex.2015 ¶¶169-173 (“Unlike Huang² above, Lee’s scaffold is also cross-linked with glutaraldehyde solution. Glutaraldehyde is ‘implicated in the development of calcification.’”); Ex.2020, 1594. Petitioner failed its burden to demonstrate that Lee’s fibers necessarily include collagen in native triple-helical form or necessarily possess less than 8 weight-percent calcium.

b) Claim 4

Lee’s generic disclosure of “high porosity” in “some embodiments” is insufficient to anticipate the claimed porosity range. Dr. Mikos’ patent regarding “shaping techniques” for a bone/cartilage matrix does not save Petitioner’s flawed contention. Dr. Mikos testifies that his patent’s porosity teachings are “not applicable” to Lee for various reasons. Ex.2015 ¶¶182-184. And even if 80% is considered “high porosity” for Mikos’ bone/cartilage matrix, (Ex.1014, 2:45-49, 13:15-17), this does not necessarily apply to Lee’s muscle scaffold, which presents different requirements. Ex.2015 ¶183 (“The appropriate porosity of those tissues varies greatly from that of the muscle tissue taught by Lee.”). By analogy, what is

considered “high porosity” in one context, e.g., a spaghetti strainer, may not translate to “high porosity” in another context, e.g., a biological cell strainer.

c) Claim 12

Neither Petitioner nor Dr. Simpson dispute the well-understood definition of “stem cell” as requiring “the capacity for both replication and differentiation.” Ex.2004, 315; Ex.1001, 1:19-23 (stem cells differentiate into different cell types, e.g., “osteoblasts, chondrocytes, ligament or tendon”); Reply 24; Ex.1219 ¶68. And neither dispute that myoblasts cannot differentiate into different cell types. To the contrary, although “myoblasts are capable of dividing and repopulating,” Ex.1011 ¶30, they cannot differentiate; they remain muscle cells. Ex.2015 ¶¶187-188. Myoblasts definitionally are not “stem cells.”

Although Dr. Simpson offers a supplemental declaration whose length exceeds that of the Reply, he never opines that myoblasts are stem cells. Ex.1219 ¶68. Instead, he points to language in Lee and Exhibit 1217 that inaccurately describe myoblasts as such, but that language is belied by the remainder of those exhibits. In fact, the record confirms that myoblasts are “committed myogenic cells” that do not differentiate into other cell types; they differentiate only into other muscle cells. Ex.1217, 459 (“Although myoblasts are committed myogenic cells, these cells can be induced to differentiate, and can stably survive in the form of hybrid myofibers. After fusion, hybrid myofibers maintain their muscle character.”);

Ex.1011 ¶¶30 (describing “[m]yoblasts” as “capable of dividing and repopulating”; they “self[-]assemble to form a more organized structure, namely muscle fibers”), 41-42; Ex.1217, 455 (myoblasts “function for growth and repair of muscle”), 456 (“stem cell-like characteristics”), 459 (“myoblasts, the precursors of muscle fibers”).

III. CONCLUSION

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

Dated: March 25, 2026

Electronic signature: / Amanda F. Wieker /
Amanda F. Wieker
Reg. No. 59,285
awieker@mcguirewoods.com

Counsel for Patent Owner LifeNet Health

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, appendix of exhibits has 5574 words as counted by Microsoft Word, the word-processing system used to prepare this response.

Dated: March 25, 2026

Electronic signature: / Amanda F. Wieker /
Amanda F. Wieker
Reg. No. 59,285
awieker@mcguirewoods.com

Counsel for Patent Owner LifeNet Health

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:

Howard Levine (Reg. No. 41,453)
David Feigenbaum (Reg. No. 78,139)
HOGAN LOVELLS US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004
howard.levine@hoganlovells.com
david.feigenbaum@hoganlovells.com

Jennifer Swan (Reg. No. 47,118)
HOGAN LOVELLS US LLP
855 Main St Suite 200
Redwood City, CA 94063
jennifer.swan@hoganlovells.com

Dated: March 25, 2026

Electronic signature: / Amanda F. Wieker /
Amanda F. Wieker
Reg. No. 59,285
awieker@mcguirewoods.com

Counsel for Patent Owner LifeNet Health