

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

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

## TABLE OF CONTENTS

|                                                                                          | Page(s) |
|------------------------------------------------------------------------------------------|---------|
| I. INTRODUCTION .....                                                                    | 1       |
| II. THE '223 PATENT .....                                                                | 2       |
| A. The '223 Patent .....                                                                 | 2       |
| 1. A scaffold comprising electrospun fibers .....                                        | 2       |
| 2. Fast Fourier transform analysis.....                                                  | 3       |
| B. The '223 Patent Claims .....                                                          | 5       |
| III. LEVEL OF SKILL IN THE ART .....                                                     | 5       |
| IV. CLAIM CONSTRUCTION .....                                                             | 6       |
| V. PETITIONER FAILS TO PROVE UNPATENTABILITY BY A<br>PREPONDERANCE OF THE EVIDENCE ..... | 9       |
| A. The Asserted Grounds and Prior Art.....                                               | 9       |
| 1. Huang2 .....                                                                          | 10      |
| 2. Lee.....                                                                              | 11      |
| 3. Kumbar.....                                                                           | 12      |
| B. Ground 1: Huang2 does not anticipate claims 1-12 .....                                | 12      |
| 1. Huang2 lacks “major peaks”.....                                                       | 12      |
| 2. Huang2 lacks “adjacent major peaks with about 180°<br>apart from each other” .....    | 16      |
| a) Dr. Simpson’s post-hoc FFT analysis is entitled to<br>no weight .....                 | 16      |
| (1) The tested image is different (and<br>insufficient) .....                            | 16      |
| (2) Huang2’s image was tested differently .....                                          | 18      |
| (3) The FFT result is different .....                                                    | 22      |
| (4) Conclusion.....                                                                      | 26      |
| b) The FFT protocol is insufficiently explained .....                                    | 26      |
| 3. Huang2 does not anticipate dependent claims 2-12 .....                                | 29      |

|     |                                                                                |    |
|-----|--------------------------------------------------------------------------------|----|
| a)  | Claim 2.....                                                                   | 29 |
| b)  | Claim 3.....                                                                   | 31 |
| c)  | Claim 4.....                                                                   | 33 |
| C.  | Ground 2: Huang2 and Kumbar do not render claim 4 obvious.....                 | 36 |
| D.  | Ground 3: Lee does not anticipate claims 1-12.....                             | 39 |
| 1.  | The Petition does not satisfy 35 U.S.C. § 312(a)(3).....                       | 39 |
| 2.  | Lee lacks “adjacent major peaks with about 180° apart<br>from each other”..... | 40 |
| a)  | Lee does not expressly disclose this limitation .....                          | 40 |
| b)  | Lee does not inherently disclose this limitation .....                         | 41 |
| c)  | Dr. Simpson’s post-hoc FFT analysis is entitled to<br>no weight .....          | 43 |
| (1) | The tested image is different (and<br>insufficient) .....                      | 44 |
| (2) | Lee’s image was tested differently.....                                        | 47 |
| (3) | Conclusion.....                                                                | 49 |
| d)  | The FFT protocol is insufficiently explained .....                             | 49 |
| 3.  | Lee does not anticipate dependent claims 2-12 .....                            | 51 |
| a)  | Claim 2.....                                                                   | 51 |
| b)  | Claim 3.....                                                                   | 53 |
| c)  | Claim 4.....                                                                   | 54 |
| d)  | Claim 12.....                                                                  | 56 |
| E.  | Ground 4: Lee does not render claims 1-12 obvious .....                        | 58 |
| 1.  | The Petition does not satisfy 35 U.S.C. § 312(a)(3).....                       | 58 |
| 2.  | The Petition does not demonstrate obviousness .....                            | 59 |
| VI. | CONCLUSION.....                                                                | 63 |

## TABLE OF AUTHORITIES

|                                                                                                                   | Page(s)    |
|-------------------------------------------------------------------------------------------------------------------|------------|
| <b>Cases</b>                                                                                                      |            |
| <i>Alnylam Pharms., Inc. v. Moderna, Inc.</i> ,<br>138 F.4th 1326 (Fed. Cir. 2025) .....                          | 6, 7       |
| <i>AMP Plus, Inc. v. DMF, Inc.</i> ,<br>131 F. 4th 1320 (Fed. Cir. 2025) .....                                    | 62, 63     |
| <i>Astrazeneca AB v. Mut. Pharm. Co.</i> ,<br>384 F.3d 1333 (Fed. Cir. 2004) .....                                | 7          |
| <i>Belden, Inc. v. Berk-Tek LLC</i> ,<br>805 F.3d 1064 (Fed. Cir. 2015) .....                                     | 60         |
| <i>Bell Atlantic Network Servs., Inc. v. Covad Comms. Grp., Inc.</i> ,<br>262 F.3d 1258 (Fed. Cir. 2001) .....    | 6          |
| <i>Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.</i> ,<br>752 F.3d 967 (Fed. Cir. 2014) .....                | 62         |
| <i>Edwards Lifesciences Corp. v. Aortic Innovations LLC</i> ,<br>IPR2023-01232, Paper 10 (PTAB Feb. 7, 2024)..... | 61         |
| <i>Harmonic Inc. v. Avid Tech., Inc.</i> ,<br>815 F.3d 1356 (Fed. Cir. 2015) .....                                | 40         |
| <i>Homeland Housewares, LLC v. Whirlpool Corp.</i> ,<br>865 F.3d 1372 (Fed. Cir. 2017) .....                      | 14, 16, 26 |
| <i>Honeywell Int’l Inc. v. 3G Licensing, S.A.</i> ,<br>124 F.4th 1345 (Fed. Cir. 2025) .....                      | 14         |
| <i>Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.</i> ,<br>821 F.3d 1359 (Fed. Cir. 2016) .....            | 43         |
| <i>Luitpold Pharms., Inc. v. Kovi</i> ,<br>IPR2018-01640, Paper 19 (PTAB Mar. 6, 2019).....                       | 26         |
| <i>In re Magnum Oil Tools Int’l, Ltd.</i> ,<br>829 F.3d 1364 (Fed. Cir. 2016) .....                               | 26         |

|                                                                                                                     |                |
|---------------------------------------------------------------------------------------------------------------------|----------------|
| <i>Med-El Elekrtomedizinische Gerate GES.M.B.H v. Sonova AG</i> ,<br>IPR2021-00023, Paper 28 (PTAB Mar. 2022) ..... | 40             |
| <i>In re Montgomery</i> ,<br>677 F.3d 1375 (Fed. Cir. 2012) .....                                                   | 42             |
| <i>Transclean Corp. v. Bridgewood Servs., Inc.</i> ,<br>290 F.3d 1364 (Fed. Cir. 2002) .....                        | <i>passim</i>  |
| <i>UiPath, Inc. v. Rule 14 LLC</i> ,<br>IPR2024-01304, Paper 8 (PTAB Mar. 14, 2025) .....                           | 61             |
| <i>Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc.</i> ,<br>97 F.4th 882 (Fed. Cir. 2024) .....             | 60             |
| <i>Vitronics Corp. v. Conceptronic, Inc.</i> ,<br>90 F.3d 1576 (Fed. Cir. 1996) .....                               | 6              |
| <i>Wilson v. Martin</i> ,<br>789 F. App'x 861 (Fed. Cir. 2019) .....                                                | 49             |
| <b>Statutes</b>                                                                                                     |                |
| 35 U.S.C. § 311 .....                                                                                               | 15, 26         |
| 35 U.S.C. § 312(a)(3) .....                                                                                         | 39, 43, 58, 62 |
| <b>Other Authorities</b>                                                                                            |                |
| 37 C.F.R. § 42.65(b) .....                                                                                          | 26, 29, 50, 51 |

## LIST OF EXHIBITS

### Patent Owner’s 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 ( <a href="https://www.zimmerbiomet.com/en/products-and-solutions/specialties/sports-medicine/tapestry-biointegrative-implant.html#06-related-product">https://www.zimmerbiomet.com/en/products-and-solutions/specialties/sports-medicine/tapestry-biointegrative-implant.html#06-related-product</a> ) |
| 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> ) |
| 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

Patent Owner LifeNet Health (“LifeNet” or “Patent Owner”) submits this Response to the Petition filed by Embody, Inc. and Zimmer Biomet Holdings, Inc. (“Petitioner”), challenging claims 1-12 of U.S. Patent Number 10,137,223 (“the ’223 patent”). Paper 2 (“Petition” or “Pet.”). The Patent Trial and Appeal Board (“PTAB” or “Board”) instituted review on August 5, 2025. Paper 14 (“Decision on Institution,” or “DI”).

Petitioner falls far short of meeting its burden to demonstrate unpatentability by a preponderance of the evidence. To the contrary, Petitioner presents primarily *anticipation* grounds even though no cited reference discloses all elements of the claims, whether expressly or inherently. Among other deficiencies, Petitioner’s Huang2 reference lacks “major peaks” which, as properly construed, require “a height higher than the average height of the peaks in the result.” Huang2 plainly lacks this element. Petitioner’s alternate reliance on its declarant’s post-hoc testing is entitled to no weight and does not cure this deficiency because that testing flatly contradicts the disclosure of Huang2 itself.

The Petition fares no better with Lee. In fact, Petitioner fails to specifically identify *any* theory of express or inherent anticipation with the reasonable particularity required by statute. As the Board preliminarily noted in its Decision on Institution, “Petitioner does not clearly assert in the Petition that the fibers taught by

Lee necessarily or inherently satisfy the FFT analysis requirement.” DI 37 (“Petitioner’s grounds based on Lee may ultimately fail on the merits due to this lack of specificity.”).

For the reasons set forth in detail below, Petitioner fails to demonstrate by a preponderance of the evidence that claims 1-12 are unpatentable.

## **II. THE ’223 PATENT**

### **A. The ’223 Patent**

#### **1. A scaffold comprising electrospun fibers**

The ’223 patent discloses a “scaffold comprising an aligned fiber.” Ex. 1001, Abstract, 13:1-7. This scaffold may be used to facilitate growth of, for example, bone, ligament, or tendon tissue, *id.* at 9:45-56, and may be incorporated into biocompatible implants used for, e.g., “tissue augmentation, contouring, restoring physiological function, repairing or restoring tissues damaged by disease or trauma, and/or delivering therapeutic agents to normal, damaged or diseased organs and tissues.” *Id.* at 15:61-65.

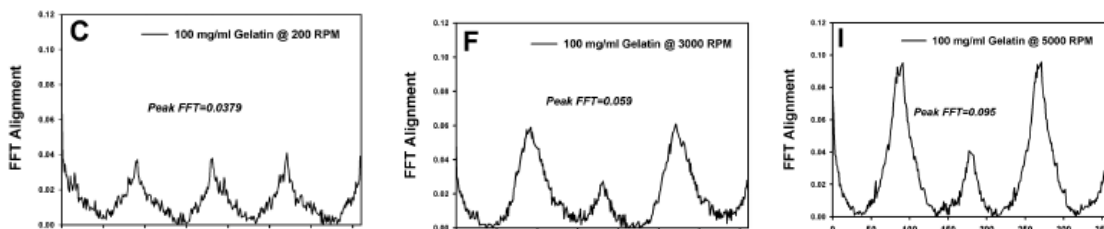
Scaffolds comprising aligned fibers may be formed by electrospinning and may be “as small as one nanometer.” *Id.* at 13:1-3, 2:17-19. The ’223 patent discloses electrospun fibers aligned in one direction and formed into an elongated roll or sheet, a composite of multiple layers of sheets, or a combination. *Id.* at 8:1-5, 8:10-16. These scaffolds may comprise collagen. *Id.* at 13:27-46.

## 2. Fast Fourier transform analysis

To measure fiber alignment, the '223 patent employs fast Fourier transform (“FFT”) analysis. *Id.* at 13:16-26. The '223 patent incorporates by reference a 2008 publication (Ex. 1010), to which Petitioner’s declarant Dr. David G. Simpson is the senior author, further describing FFT analysis. *Id.*; Pet. 12, 30; Ex. 1003 ¶ 61.

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

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



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

aligned elements exhibit asymmetrical peaks, two larger peaks at 90 and 270° and two smaller peaks at 0 and 360° (Fig. 1F and I).” *Id.* at 610.

A FFT analysis result conveys information about the analyzed fibers. For example, “the height and overall shape of the most prominent peaks present in the alignment plot” conveys “[t]he degree of alignment present in the original data image”; the shape of the peak conveys the uniformity of fiber alignment, where “[a] high and narrow peak indicates a more uniform degree of fiber alignment, [but] a broad peak, or a shoulder on the peak indicates that more than one axis of alignment may be present”; and, finally, “the principal axis of fiber alignment is determined by the position of the alignment peaks.” Ex. 1010, 610 (emphases added); Ex. 1003 ¶¶ 41-42.

The '223 patent explains that the FFT analysis result of the claimed scaffold shows “adjacent major peaks with about 180° apart from each other,” where “major peaks” “refer to peaks higher than the average of the peaks in the result.” Ex. 1001, 13:3-7. This is depicted in Figure 8A, reproduced below alongside Figure 8B.

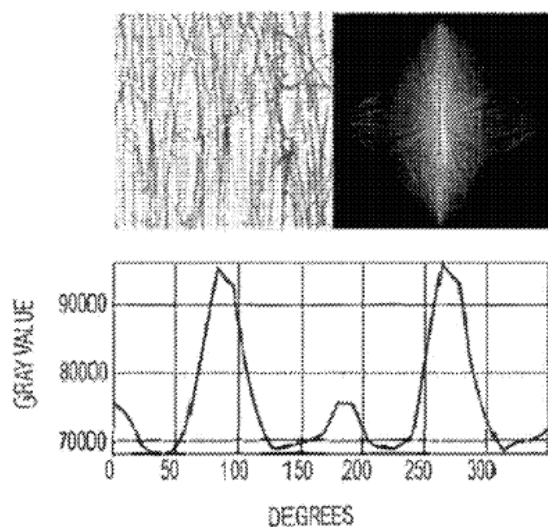


**FIG. 8A**

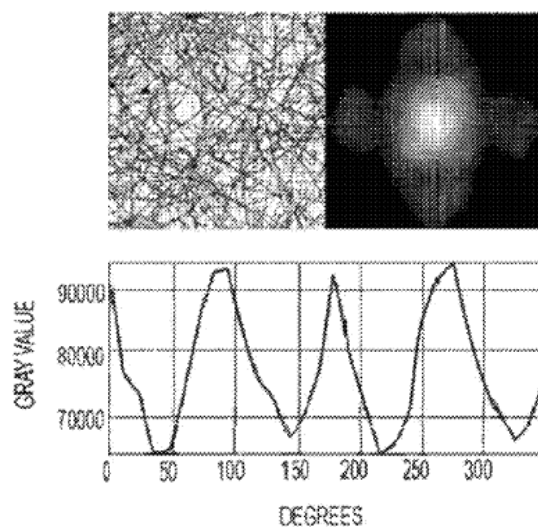


**FIG. 8B**

*Id.* at 13:24-26, Figs. 8A-8B. “FIG. 8 depicts exemplary FFT analysis results (a) of the [aligned] fibers described herein and (b) a control sample.” *Id.* at 1:56-57. As shown, aligned fibers show “adjacent major peaks with about 180° apart from each other” (Figure 8A), while non-aligned fibers do not (Figure 8B). *Id.* at 13:24-26.

## **B. The '223 Patent Claims**

Claims 1-12 are challenged. Pet. 1. Claim 1 is independent and 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.

## **III. LEVEL OF SKILL IN THE ART**

Patent Owner generally does not dispute Petitioner’s identified level of skill possessed by a person of ordinary skill in the art (“POSITA”), however, Patent

Owner clarifies that a POSITA would have earned their Ph.D. in bioengineering, chemical engineering, mechanical engineering, or a related engineering discipline. Pet. 18-19; Ex. 2015 ¶ 39. Patent Owner’s declarant, Dr. Mikos, meets both Petitioner’s and Patent Owner’s definition. Ex. 2015 ¶ 40.

#### IV. CLAIM CONSTRUCTION

Claim construction is necessary here. *Contra* Pet. 19.

Independent claim 1 recites: “major peaks.” Ex. 1001, 23:6-9. Here, the patentee provided an express definition of “major peaks” in the ’223 patent: “‘major peaks’ herein refer to peaks higher than the average of the peaks in the result.” *Id.* at 13:6-7.

A patentee may “be his own lexicographer ... as long as the special definition of the term is clearly stated in the patent specification or file history.” *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). To determine whether a term is definitional, “the intrinsic evidence must ‘clearly set forth’ or ‘clearly redefine’ a claim term so as to put [a POSITA] on notice that the patentee intended to so redefine the claim term.” *Bell Atlantic Network Servs., Inc. v. Covad Comms. Grp., Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001) (citation omitted)

Here, the ’223 patent’s Specification clearly meets this definitional standard. Ex. 1001, 13:6-7. In particular, the term “major peaks” “is set off in quotation marks,” indicating that it is definitional. *Alnylam Pharms., Inc. v. Moderna, Inc.*,

138 F.4th 1326, 1333 (Fed. Cir. 2025). The definitional sentence also uses “‘refer to,’ which generally conveys an intent for [that sentence] to be definitional.” *Id.* Further, this language is unqualified and does not use “non-limiting terms” that detract from its definitional nature, such as “e.g.” or “for example.” *Id.*

Finally, although “it is ... improper to limit the claims to the particular preferred embodiments ..., the patentee’s choice of preferred embodiments can shed light on the intended scope of the claims.” *Astrazeneca AB v. Mut. Pharm. Co.*, 384 F.3d 1333, 1340 (Fed. Cir. 2004). Here, the only disclosed embodiment of “major peaks” is shown in Figure 8A below and matches the Specification’s express definition.

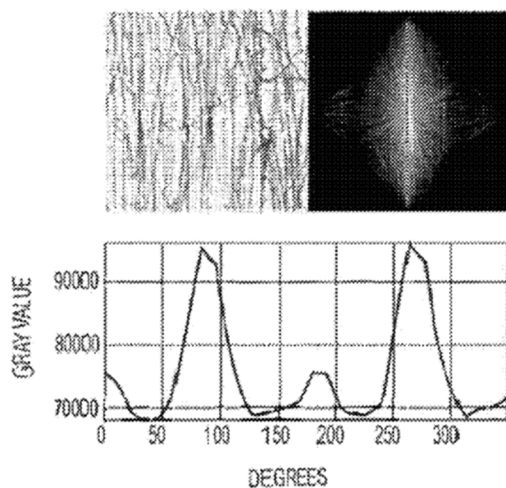


**FIG. 8A**

Ex. 1001, Fig. 8A, 13:24-26. As shown in Figure 8A, the peaks that occur at 90° and 270° are “major peaks” as defined. Indeed, their height is higher—peaking at approximately 95,000 units—than the average height of the four peaks shown in

the result. Ex. 2015 ¶ 56 (explaining that four peaks are depicted in the result with those appearing at 0° and 180° having a height of 95,000, and those appearing at 90° and 270° having a height of 75,000, such that the average height of the four peaks is approximately 85,000 units).

Dr. Mikos testifies that the Specification's definition of "major peaks" is consistent with how a POSITA would have understood the term. *Id.* ¶ 57. Dr. Mikos explains that the "FFT process plots the high frequency signals in the image, which reflect fiber alignment, as prominent or 'major' peaks that depict the extent of fiber alignment." *Id.* (citing Ex. 1010, 610). Those are necessarily higher than the average heights of all peaks in the FFT result because the FFT analysis will also depict smaller peaks which reflect lower frequency signals. *Id.* ¶ 58.

During his deposition, Petitioner's declarant Dr. Simpson agreed that a "way to describe a major peak [would] be that its height is higher than the average heights of the peaks in the plot." Ex. 2017, 89:3-9 (also agreeing that "major" is a relative term). This is consistent with Dr. Simpson's prior statements. *See, e.g.*, Ex. 1010, 610 ("The degree of alignment present in the original data image [for sample scaffolds containing aligned elements] is reflected by the height and overall shape of the most prominent peaks present in the alignment plot. A high and narrow peak indicates a more uniform degree of fiber alignment."), 615 ("The larger peaks report the principle axis of alignment while the smaller peaks correspond to background

information, noise and edge effects.”); Ex. 1003 ¶¶ 40-41 (describing FFT).

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

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

### **A. The Asserted Grounds and Prior Art**

Petitioner presents the following grounds. Pet. 5.

| <b>Claim(s) Challenged</b> | <b>35 U.S.C.</b> | <b>Reference(s)</b>         |
|----------------------------|------------------|-----------------------------|
| 1-12                       | § 102            | Huang2 <sup>1</sup>         |
| 4                          | § 103            | Huang2, Kumbar <sup>2</sup> |

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

<sup>2</sup> Kumbar et al., *Electrospun nanofiber scaffolds: engineering soft tissues*, BIOMED. MATER. 3 (2008) (“Kumbar,” Ex. 1006).

|      |       |                  |
|------|-------|------------------|
| 1-12 | § 102 | Lee <sup>3</sup> |
| 1-12 | § 103 | Lee              |

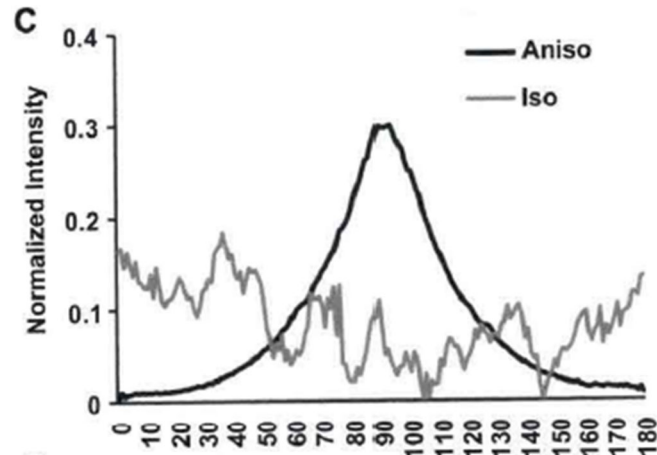
## 1. Huang2

Huang2 discloses scaffolds for skin tissue repair. Ex. 1005, Abstract. Huang2 explains that, “[t]o better support and facilitate skin cells to form skin-like tissues, it is necessary for the temporary scaffolds not only to provide a surface for the cells to reside, but also to define a cell-friendly microenvironment that maximally recaptures the native extracellular matrix (ECM).” *Id.* at 1791. Accordingly, Huang2 provides an electrospun scaffold made from a blend of collagen and polycaprolactone (“PCL”). *Id.*

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

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



Huang2's Figure 1C depicts "[n]ormalized intensity plots against the angle of acquisition for isotropic and anisotropic nanofibrous matrices," plotted from 0° to 180° degrees, where aligned fibers present a single peak.<sup>4</sup> *Id.* at 1793. Huang2 explains that "[t]he narrow peak ... indicated that PCL/Coll nanofibers aligned along a single axis (Fig. 1B)." *Id.* at 1794.

## 2. Lee

Lee discloses scaffolds for muscle tissue repair. Ex. 1011, Abstract. Lee explains that "it is preferable to mimic native skeletal muscle construction, with its highly-oriented fibers of fused mononucleated muscle cells." *Id.* ¶ 4. To that end, Lee discloses "muscle implants including: a biodegradable scaffold comprising a plurality of fibers oriented along a longitudinal axis of the fibers." *Id.* ¶ 5. The

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<sup>4</sup> Huang2 defines "isotropic" as "fibers collected randomly with no alignment" and "anisotropic" as "fibers collected with alignment." Ex. 1005, Abstract.

scaffold may comprise electrospun collagen, optionally with polymers like PCL. *Id.* ¶ 6.

### **3. Kumbar**

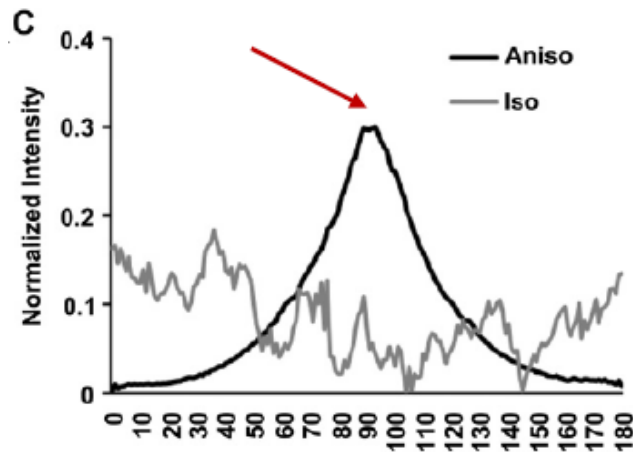
Kumbar creates electrospun nanofibers that “show morphological similarities to the natural extra-cellular matrix.” Ex. 1006, 2. Because “[e]lectrospun nanofiber matrices present a dynamic system in which the pore size and shape can change when compared to other rigid porous structures,” Kumbar discloses different electrospun nanofibers with different porosities. *Id.* at 7-8. For example, the porosity of fibers consisting of PLAGA was 91.63% (*id.* at 7), collagen type I was 89% (*id.* at 8), cross-linked collagen type I was 71% (*id.*), and silk fibroin was 76.1% (*id.*). Kumbar teaches that “porosity and pore-size distribution greatly depend on ... parameters selected for electrospinning,” such as “polymer molecular weight[ and] polymer solution properties.” *Id.* at 4, 5 (“[P]olymer and polymer solution properties play a significant role in controlling the fiber diameter and structural morphology.”).

### **B. Ground 1: Huang2 does not anticipate claims 1-12**

#### **1. Huang2 lacks “major peaks”**

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

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

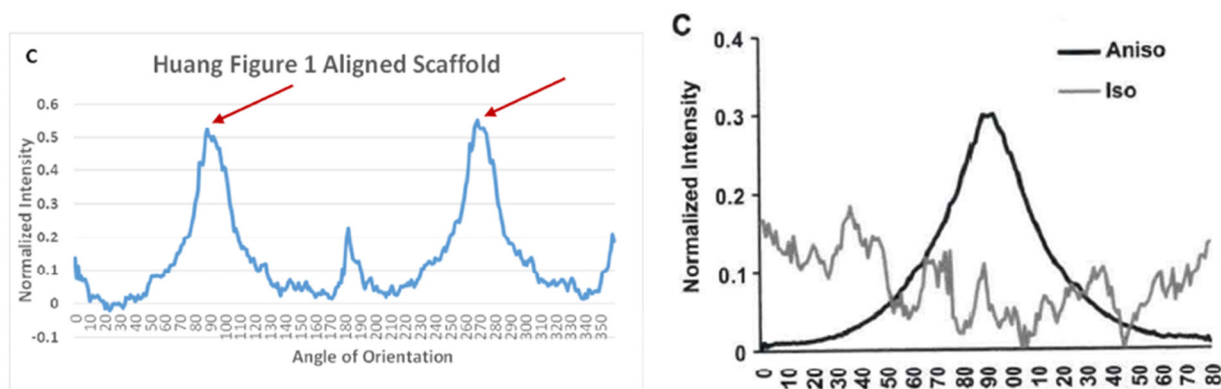


Pet. 30-31; Ex. 1005, 1794 (“[t]he narrow peak”). Because only one peak is disclosed, that sole peak controls the average height of the peaks in the result. In other words, the height of the sole peak *is identical to*—not higher than—the average height of the peaks in the result. The height of both the sole peak and the average are the same: 0.3 Normalized Intensity units. Ex. 2015 ¶ 66 (“With a single peak reported by Huang2, and no smaller ‘minor’ peaks, the average height would be the same value as the single peak: 0.3 Normalized Intensity units as shown in the figure above.”); Ex. 1005, 1793 (Fig. 1C). Accordingly, Huang2’s single peak is not a “major peak” as claimed because its height is not higher than the average height of the peaks in the result. *Id.* ¶ 67.

Petitioner also relies upon a FFT plot created by Dr. Simpson’s post-hoc testing of a reproduced image of Huang2’s fibers. Pet. 31-33. As discussed below and incorporated herein, Dr. Simpson’s testing deviated from the FFT protocol applied by Huang2 and conflicts with Huang2’s results; it should not be considered.

*See infra* § V.B.2.a (discussing other deviations); Ex. 2015 ¶ 68 (“[A] POSITA would not credit the post-hoc testing performed by Dr. Simpson over the authors’ own published FFT analysis result.”).

Moreover, Dr. Simpson’s testing produced a FFT result that directly conflicts with Huang2’s disclosure. As shown below, Dr. Simpson’s testing depicts two minor peaks in the FFT plot, at 0° and 180°, that are *absent* and not disclosed by Huang2. Compare Ex. 1003 ¶ 110, with Ex. 1005, Fig. 1C; see Ex. 2015 ¶ 69.



Dr. Simpson’s post-hoc FFT plot is “plainly inconsistent” and “flatly contradicted” by Huang2 itself, which expressly discloses a FFT plot *without any* additional peaks. Dr. Simpson’s inconsistent result should not be considered because it 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.”); *Honeywell Int’l Inc. v. 3G Licensing, S.A.*, 124 F.4th 1345, 1354 n.6 (Fed. Cir. 2025) (“[O]n its face, this statement conflicts with the plain language of the

Philips reference .... [W]e are not required to uncritically accept expert testimony that is flatly contradicted by the record.”). As Dr. Mikos testifies, “a POSITA would credit the Huang2 reference itself and would not credit Dr. Simpson’s post-hoc testing, which conflicts with Huang2’s disclosure, in part because Huang2 performed more reliable FFT analysis than Dr. Simpson did,” as Dr. Mikos explains further in his declaration. Ex. 2015 ¶ 70 (citing *id.* § IV.B.1.a.2); *see infra* § V.B.2.

It is Petitioner who chose to rely upon Huang2, and it is Petitioner who chose to assert anticipation. Petitioner now bears the burden of proving anticipation by a preponderance of evidence. It cannot meet that burden by, on the one hand, relying on Huang2 for *some* limitations of the claim while, on the other, asking the Board to ignore Huang2’s disclosure and instead rely upon contradictory extrinsic evidence to suggest other limitations. This is an anticipation ground and Petitioner is wedded to its choices. *See Application of Turlay*, 304 F.2d 893, 899 (C.C.P.A. 1962) (“It is well established that an anticipation rejection cannot be predicated on an ambiguous reference”).

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

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

Here, the printed publication upon which Petitioner relies for anticipation depicts a FFT result without *any* additional peaks and, accordingly, lacks “major peaks” as properly construed. Ex. 2015 ¶¶ 63-71. For these reasons, Huang2 does not anticipate independent claim 1.

**2. Huang2 lacks “adjacent major peaks with about 180° apart from each other”**

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

To support its allegation that Huang2 anticipates this limitation, Petitioner relies upon Dr. Simpson’s post-hoc testing and alleges that this demonstrates “adjacent major peaks” as claimed. But this testing is entitled to no weight.

Dr. Simpson states that he “conducted [his] own analysis of Figure 1B using the FFT analysis described in Huang2 and the ’223 patent.” Ex. 1003 ¶ 110. This is incorrect. Dr. Simpson’s testing is plainly inconsistent with “the FFT analysis described in Huang2” and, therefore, cannot credibly interpret Huang2’s disclosure. *Homeland Housewares*, 865 F.3d at 1378 (“[W]e must disregard the testimony of an expert that is plainly inconsistent with the record.”).

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

Dr. Mikos testifies that “[i]mage quality is the single most important factor in

FFT testing.” Ex. 2015 ¶ 77 (“Poor image quality that lacks sufficient contrast, resolution, and/or brightness results in invalid and inaccurate test results.”); *see also* Ex. 2017, 58:25-59:18 (Dr. Simpson explaining that image acquisition is the most important step in FFT analysis), 142:14-15 (“You should always be collecting data with the best capability that you have.”); Ex. 1003 ¶ 184 (Dr. Simpson discarding one image to instead rely upon “higher quality images”). Without a sufficient image, FFT testing results cannot be credited. Ex. 2015 ¶ 77.

Here, however, Dr. Simpson did not test high quality images of the type he typically analyzes. Instead, Dr. Simpson performed FFT analysis on an Adobe PDF reproduction of Huang2’s SEM image. Ex. 2017, 138:23-139:16 (Dr. Simpson stating that he tested a downloaded PDF image), 157:8-14 (Dr. Simpson stating that testing a photocopied image is “not something I do routinely”); Ex. 2015 ¶ 76 (“Dr. Simpson did not test SEM images themselves as is customary and accepted in the field.”).<sup>5</sup> Performing FFT analysis on a reproduction of a SEM image can lead to invalid and inaccurate results. Ex. 2015 ¶ 78.

For example, reproduced images like that used by Dr. Simpson introduce

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<sup>5</sup> Dr. Simpson did not document or account for any image compression performed on the image when converting it to PDF form. *Id.*

noise, blur, and uneven illumination to the analysis. *Id.* Image contrast is necessarily reduced and fine details—which are essential to a reliable FFT result—are lost. *Id.* (“A POSITA would not find a reproduced or photocopied image to be suitable for FFT analysis.... Reproductions introduce noise, blur, and/or uneven illumination.”); Ex. 1010, 609 (Dr. Simpson acknowledging that uneven illumination introduces error); Ex. 2017, 163:24-164:2 (Dr. Simpson recognizing that an image may be “so degraded by being Xeroxed”). Dr. Mikos testifies that the noise and artifacts present in reproduced images adversely affect FFT plot shape with high frequency features, which reflect fiber orientation, most affected. Ex. 2015 ¶ 78; Ex. 1010, 612 (Dr. Simpson acknowledging that noise introduces artifacts into the FFT result).

In fact, both Dr. Mikos and Dr. Simpson testified that they do not normally perform FFT analysis with reproduced or photocopied images. *Id.* ¶ 78 (“I have never performed FFT testing with a reproduced or photocopied image.”); Ex. 2017, 157:8-14 (“Q. So you don’t normally do that? A. No.”), 157:23-158:3 (Dr. Simpson testifying that he does not advise his students to test reproductions).

## **(2) Huang2’s image was tested differently**

Despite stating that he “us[ed] the FFT analysis described in Huang2,” Ex. 1003 ¶ 110, Dr. Simpson did not. To perform FFT analysis, Huang2 obtained SEM “images of *five* randomly selected areas” of the scaffold. Ex. 1005, 1792 (emphasis added). “Representative SEM images of the electrospun fibers were

cropped into a square covering as much of the image as possible.” *Id.* Huang2 then performed FFT analysis “on the SEM images of [the] randomly selected areas ( $n = 5$ ).” *Id.* at 1794. But this is not the FFT analysis that Dr. Simpson performed. Instead, Dr. Simpson “cropped and masked” a copy of a *single* SEM image (i.e., a reproduction of Huang2’s Figure 1B) and used that single *masked* image for FFT analysis. Ex. 1003 ¶ 110 (figures and caption); Ex. 2017, 137:2-5 (Dr. Simpson agreeing that “Huang 2 performed FFT based on five images of randomly selected areas of its scaffold” and that Figure 1B image is only one such image).

First, as Dr. Simpson acknowledged during his deposition, he “misinterpreted” Huang2’s disclosure and incorrectly “believe[d] that [Huang2] used a mask” when, in fact, Huang2 did not. Ex. 2017, 144:11-13. Given that misinterpretation, Dr. Simpson incorrectly applied a mask in his FFT analysis of Huang2’s image. *Id.* at 146:11-12 (“I used a circular mask because I misread that sentence.”). As clearly disclosed, however, Huang2 did not utilize a mask. Ex. 2015 ¶ 80. Huang2 states that “representative SEM images of the electrospun fibers were cropped into a square ... then processed with a fast Fourier transform (FFT) and then a circular selection of the image was made ... [which] underwent a radial summation”; no mask was used in Huang2’s FFT analysis. Ex. 1005, 1792. Moreover, Huang2 cites to Dr. Simpson’s 2006 paper (Ex. 1013), which *also* did not

employ a mask. Ex. 1005, 1792 (citing [22]), 1800; *see generally* Ex. 1013.<sup>6</sup>

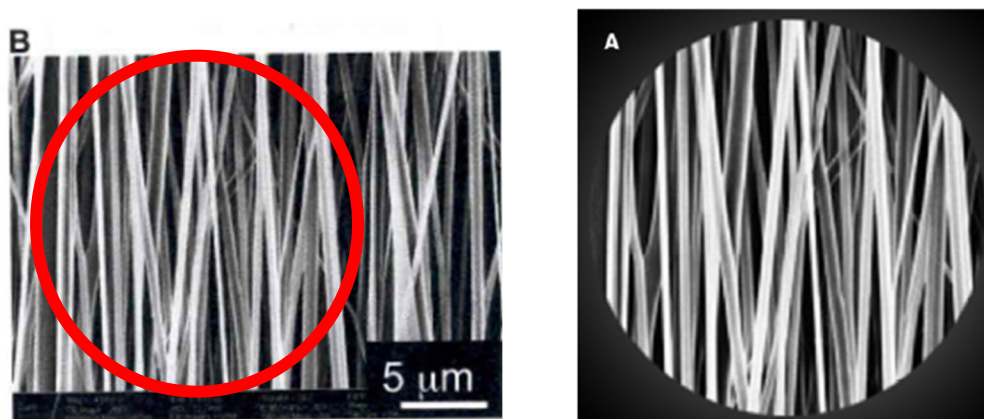
Inclusion or exclusion of a mask *directly* impacts the resulting FFT plot, as Dr. Simpson’s 2008 paper explains. As reported there, for example, when performing FFT analysis on fibers oriented at 45°, the FFT plot included “edge noise” that appeared as small peaks in the FFT plot. Ex. 1010, 615. In particular, “[t]he unmasked image produces a 2D FFT alignment plot with artifacts in the guise of small peaks on either side of the alignment peaks (Fig. 3N, arrows).” *Id.* But the paper explains that “[p]rocessing the image with a window mask removes this spurious information without altering the height of the alignment peaks.” *Id.* In other words, inclusion or exclusion of a mask is not a trivial detail. Ex. 2015 ¶ 84.

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<sup>6</sup> During his deposition but regarding Lee, *see infra* § V.D.2, Dr. Simpson contended that use of a mask is consistent with his 2008 paper (Ex. 1010). Ex. 2017, 163:16-164:5. But the 2008 paper is not incorporated in Huang2. Moreover, the 2008 paper discloses an *optional* mask, an option that was not exercised in the ’223 patent. Ex. 1001, Fig. 8A (depicting the tested image without a mask). As noted by Dr. Simpson, exercising this option comes at the expense of “reduc[ing] the total surface area available for analysis.” Ex. 1010, 615. Regardless, there is no dispute that Huang2 does *not* disclose a mask.

Indeed, adding or omitting a mask directly impacts the resulting FFT plot and results in different peaks being included. *Id.* (applying a “mask will result in different peaks being included or excluded”).

Second, while Huang<sup>2</sup> performed FFT analysis on *five* representative images, Dr. Simpson tested only a single image. On top of that, Dr. Simpson’s improper use of a mask discarded a large portion of the *single* image that he tested, as shown below.



Ex. 1005, 1793 (left, annotated with a red circle to approximate the mask applied by Dr. Simpson); Ex. 1003 ¶ 110 (right, the single masked image that Dr. Simpson tested); Ex. 2015 ¶ 82.

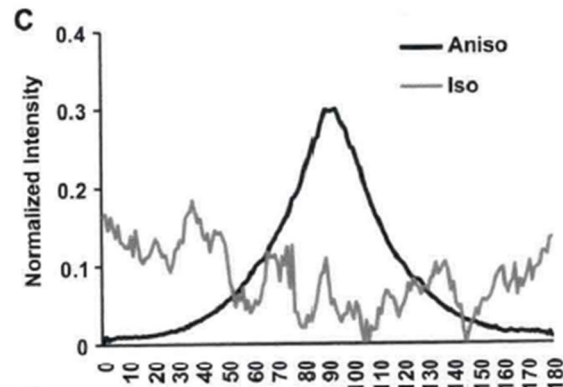
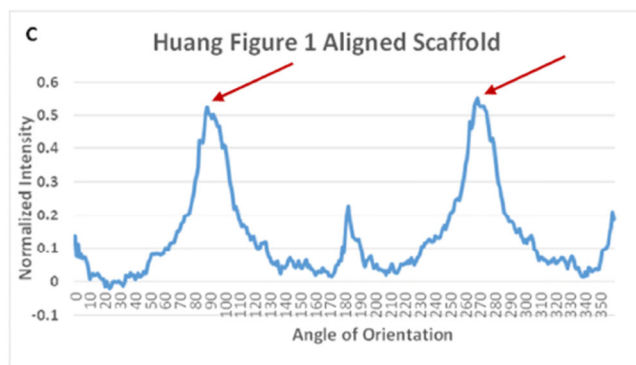
Dr. Simpson’s approach here violates his own past practice. In his 2008 paper, for example, Dr. Simpson admonished: “measurements of scaffold anisotropy should be averaged over as large as an area as possible.” Ex. 1010, 606. This is precisely because “[l]ocal variations in fiber alignment *can bias the 2D FFT*

*process.” Id.* (emphasis added). Accordingly, to avoid biasing the results, Dr. Simpson previously recommended that “alignment data can be *captured from several sites in a scaffold and averaged* to circumvent the limitations inherent when a small sample surface area must be used to generate an alignment value.” *Id.* (emphasis added). Dr. Simpson took no such efforts here to avoid FFT results that are biased by the small area that he tested. Ex. 2015 ¶ 83 (“A POSITA would recognize that Dr. Simpson’s testing would produce inaccurate results because he utilized such a small portion in his testing.”).

Despite his statement to the contrary, Dr. Simpson did *not* perform the FFT analysis described in Huang2 and, in doing so, also violated his own past statements regarding the importance of testing a sufficiently representative sample.

### **(3) The FFT result is different**

Dr. Simpson’s resulting FFT plot *is not the same* as that disclosed by Huang2. This result varies in three manifest respects, each casting doubt on the validity of Dr. Simpson’s FFT analysis. Dr. Simpson’s FFT plot and Huang2’s FFT plot are reproduced below, side by side.



Compare Ex. 1003 ¶ 110, with Ex. 1005, 1793.

Dr. Simpson’s testing (left above) produced a markedly different result than Huang2 (right above) even putting aside that Dr. Simpson plotted his testing to 360°. Ex. 2015 ¶ 87. First, while Huang2’s FFT plot depicts a broad curve that extends from 0° to 180°, Dr. Simpson’s FFT plot depicts a much narrower curve, extending at most from 20° to 140°. *Id.* ¶ 88. Second, while Huang2’s peak reaches a maximum height of 0.3 normalized intensity units, Simpson’s peaks extends 83% higher, to 0.55 normalized intensity units. *Id.* ¶ 89. Third, as detailed above, *see supra* § V.B.1, while Huang2’s FFT lacks any minor peaks, Simpson’s FFT depicts two, at 0° and 180°. *Id.* ¶ 90. In short, these FFT analyses convey fundamentally *different* results and, accordingly, convey fundamentally *different* information about the underlying fibers. *Id.* ¶ 91.

As discussed above, the height and overall shape of the most prominent peaks convey the degree of fiber alignment, where “[a] high and narrow peak indicates a more uniform degree of fiber alignment, [but] a broad peak, or a shoulder on the

peak indicates that more than one axis of alignment may be present.” Ex. 1010, 610; Ex. 2015 ¶ 88; *see supra* § II.A.2. Dr. Simpson made clear during his deposition that these are relative terms; a peak may be deemed “narrow” or “broad” only in relation to other peaks. Ex. 2017, 99:2-7 (explaining that “high and narrow” is “a relative description between those two samples”), 100:13-14 (“It’s only broad relative to a peak that is -- that it could be compared to.”). And, to that end, Dr. Simpson testified that he normalized his FFT plot precisely so that it could be compared against Huang2’s FFT plot. *Id.* at 166:1-11 (explaining that he normalized his testing data because “I was comparing Huang to Huang.”). But, despite having normalized his data, Dr. Simpson fails to reconcile the notable differences that appear in his FFT plot as compared to Huang2’s.

In reviewing the FFT plot shapes achieved by Dr. Simpson’s testing as compared to Huang2’s, even when normalized, they present inconsistent findings. Specifically, the relatively “high and narrow peak” depicted in Dr. Simpson’s testing shows “a more uniform degree of fiber alignment” (Ex. 1010, 610) than that reported by Huang2. Ex. 2015 ¶ 88; *compare* Ex. 1003 ¶ 110, *with* Ex. 1005, 1793. By contrast, Huang2’s relatively shorter and broader peak conveys “that more than one axis of alignment may be present” (Ex. 1010, 610). Ex. 2015 ¶ 88. Petitioner fails to address these differences, let alone explain them. *Id.* ¶ 88 (“Given that both sets of FFT results purport to reflect the same set of fibers from the same image, this

discrepancy alone renders Dr. Simpson's results unreliable.").

And in reviewing the FFT plot heights achieved in Dr. Simpson's testing as compared to Huang2's reported results, they also present inconsistent findings. Ex. 2015 ¶ 89. Dr. Simpson previously stated that "the onset of anisotropic properties in an electrospun scaffold ... [appears] at a threshold alignment value of 0.05 units. For example, the stress at failure for a random scaffold (Fig. 1C) of electrospun gelatin (2D FFT alignment value <0.05 units) is approximately 0.5 MPa in all directions. Once alignment values of 0.05 units are detected [in] this type of scaffold, stress at failure will increase incrementally as a function of approximately 0.01 2D FFT alignment units." Ex. 1010, 610. Accordingly, anisotropic properties for Huang2's fibers, like stress at failure, would be notably higher based on Dr. Simpson's testing (0.55 normalized units) than for Huang2's reported results (0.3 normalized units), which again renders Dr. Simpson's testing unreliable. Ex. 2015 ¶ 89. Again, as these FFT plots purport to reflect the same fibers, this discrepancy renders Dr. Simpson's testing unreliable. *Id.*

And, as discussed above, the presence of minor peaks in Dr. Simpson's FFT result, which are affirmatively absent from Huang2's FFT result, presents yet another inconsistency in Dr. Simpson's FFT plot. Given that both sets of FFT results purport to reflect the same set of fibers from the same image, this discrepancy alone renders Dr. Simpson's results unreliable. *Id.* at ¶ 90.

Given these notable differences in FFT results, a POSITA would recognize that Dr. Simpson's FFT testing conveys fundamentally *different* information about the underlying fibers than Huang2 itself disclosed. Accordingly, a POSITA would disregard Dr. Simpson's testing. Ex. 2015 ¶ 91.

#### **(4) Conclusion**

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

##### **b) The FFT protocol is insufficiently explained**

With this background of conflict and inconsistency, Dr. Simpson's bare statement that he “conducted [his] own analysis of Figure 1B using the FFT analysis described in Huang2 and the '223 patent” is insufficient to satisfy 37 C.F.R. § 42.65(b). *Luitpold Pharms., Inc. v. Kovi*, IPR2018-01640, Paper 19 at 23-24 (PTAB Mar. 6, 2019) (finding insufficient an expert declaration that “fails to provide any specificity as to the steps taken”).

Dr. Simpson testified that a POSITA typically documents the steps taken in

performing an FFT analysis, and that Dr. Simpson *required* that his students do so. Ex. 2017, 59:19-60:8 (“[Y]ou would certainly document the parameters that you’re using so you can reproduce them over and over and over and over and over again.”), 60:19-23; Ex. 2015 ¶ 92 (“[I]t is customary for a POSITA to document all aspects of their testing such that others may evaluate the test results in view of the protocol employed and, if desired, reproduce those results.”).

Dr. Simpson’s declaration, however, does not even identify the *version of software* he used to conduct his analysis, let alone the parameters he applied in testing a reproduction of Huang2’s image. Ex. 2017, 140:24-141:4. Likewise, Dr. Simpson did not document where or how he applied the circular projection in the ImageJ software to generate his FFT plot, a “critical” aspect of FFT analysis. *Id.* at 150:10-18; Ex. 2015 ¶ 94 (“If the circular selection does not capture a representative portion of the FFT output image, it will bias the results.”). With this vacuum of information, reproducing Dr. Simpson’s testing is impossible. Ex. 2015 ¶ 95. Petitioner cannot meet its burden by relying upon testing undertaken with a mystery and non-reproducible protocol.

Dr. Simpson’s earlier paper, incorporated by reference into the ’223 patent, describes other critical aspects of FFT analysis that are essential to accurate testing, that were not accounted for in Dr. Simpson’s testing, and which *directly impact* both the validity of FFT testing and the shape of the resultant FFT plot.

For example, Dr. Simpson's earlier paper emphasizes the importance of image quality to reliable FFT testing. In his 2008 paper, Dr. Simpson utilized images that were "stored and analyzed as uncompressed .TIF files to preserve image integrity [precisely because] the image compression used in .JPG format will degrade image integrity." Ex. 1010, 607. In his post-hoc testing, however, Dr. Simpson "ha[d] no idea" how Huang2's image was stored and did not attempt to account for that in his analysis. Ex. 2017, 140:17-19; Ex. 2015 ¶ 96.

Likewise, in 2008, Dr. Simpson identified risks associated with uneven illumination of an image: "Care should be taken at the time of image capture to optimize sample illumination; uneven illumination can complicate and introduce error into the alignment analysis." Ex. 1010, 609. Again, here, Dr. Simpson "ha[d] no idea" if sample illumination was optimized for Huang2's image and did not attempt to improve the image's illumination. Ex. 2017, 135:14-19; Ex. 2015 ¶ 97.

And, despite previously recognizing the impact of optical and electronic noise on FFT analysis, Ex. 1010, 609, Dr. Simpson did not account for the presence of such noise in his reproduction of Huang2's figure. Ex. 2015 ¶ 98.

As discussed by Dr. Mikos and above, *see supra* § V.B.2.a.1, testing a reproduced image, like Dr. Simpson did here, detracts from the image quality that is so important to FFT testing. Ex. 2015 ¶ 99. Testing a reproduction introduces noise, blur, and/or uneven illumination, all of which adversely affect the resulting FFT plot

shape. High frequency features of the FFT plot, which reflect alignment of the fibers, will be most affected. *Id.* Again, it was Petitioner’s burden to demonstrate anticipation; that burden cannot be satisfied with incomplete, undisclosed, and non-reproducible post-hoc testing that violates 37 C.F.R. § 42.65(b).

Quite simply, Dr. Simpson’s results cannot be credited. Ex. 2015 ¶¶ 92-104 (also discussing the impact of normalization and masking, discussed *supra* § V.B.2.a). For these reasons, Huang2 does not anticipate independent claim 1.

### **3. Huang2 does not anticipate dependent claims 2-12**

Dependent claims 2-12 include all limitations of independent claim 1 and, for the same reasons articulated above, Petitioner’s contentions likewise fail.

#### **a) Claim 2**

Dependent claim 2 further recites that “the fibers comprise type I collagen in its native triple helical structure.” Ex. 1001, 23:10-11. Petitioner contends that Huang2 uses type I collagen, which was known to have triple-helical form, lest it would have been called gelatin. Pet. 33.

Huang2 is silent as to the form of collagen in its fibers and, therefore, does not expressly anticipate. Ex. 2015 ¶ 107 (“[Huang2] does not specify the structure of the collagen that is present in the resulting electrospun fibers themselves.”). Nor is this limitation inherent because Huang2 does not “necessarily include the unstated limitation.” *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed.

Cir. 2002). A POSITA would have understood that, given the materials used in Huang2's electrospinning and cell culture processes, its fibers do *not* necessarily possess collagen in its native triple helical structure. Ex. 2015 ¶ 108 ("A POSITA would have readily understood that many compounds," including several disclosed by Huang2, "cause type I collagen to denature out of its native triple helix.").

For example, Dr. Mikos testifies that PCL and 1,1,1,3,3,3-hexafluoro-2-propanol ("HFIP"), both used by Huang2 to electrospin its fibers, *necessarily* denature Huang2's collagen. Ex. 2015 ¶ 109; Ex. 1005, 1792 ("dissolving PCL and collagen in HFIP"). Specifically, both PCL and HFIP disrupt the hydrogen bonds and other interactions that keep collagen in its native triple helical structure. Ex. 2015 ¶ 110 (explaining that blending PCL with collagen renders the blend hydrophilic which slightly accelerates PCL's degradation, thereby releasing acidic byproducts, decreasing pH, and causing collagen to denature); Ex. 2018, 1224, Fig. 5 (depicting the "degradation of PCL via hydrolysis" with 6-hydroxycaproic acid). The denaturing of collagen out of triple helical form is amplified by Huang2's use of fetal bovine serum ("FBS") when culturing cells on the scaffold because FBS also degrades PCL, further disrupting the bonds that keep collagen in its native triple helical structure. Ex. 2015 ¶ 111; Ex. 1005, 1792 (cell culture medium "supplemented with 10% fetal bovine serum").

In fact, POSITAs routinely avoid HFIP precisely because it denatures

collagen. Ex. 2015 ¶ 112 (“HFIP engages in hydrophobic and hydrophilic interactions, which unfold the triple helix by interfering with the hydrogen bonds that maintain collagen in its native triple helical structure.”). Contemporaneous publications confirm this fact: “Electro-spinning collagen out of fluoroalcohols [like HFIP] denatures collagen to gelatin.” Ex. 2019, 2303; *see also id.* at Abstract (“[T]he very properties that have established collagen as the leading natural biomaterial are lost when it is electrospun into nanofibres out of [HFIP].”), 2294 (“[E]lectro-spinning of collagen ... out of fluoroalcohols results in the creation of gelatin, a protein derived from denatured collagen and is characterized by ... disrupted triple-helical and fibrillar structure.”); Ex. 2015 ¶ 113.

Accordingly, a POSITA would have known that the type I collagen used in Huang2’s electrospinning process would have denatured such that the resulting fibers would *not* necessarily comprise collagen in its native triple helical structure. Petitioner has not met its burden to demonstrate inherency. Ex. 2015 ¶¶ 114-115.

**b) Claim 3**

Dependent claim 3 further recites that “the fiber has less than about 8 wt % residual calcium.” Ex. 1001, 23:12-13. Petitioner contends that Huang2 anticipates this claim because it “does not indicate any calcium was used” and “did not ‘incorporate’ or otherwise use calcium in the production of these fibers.” Pet. 34.

Huang2 is silent as to the percent weight of residual calcium and, therefore, does not expressly anticipate. Ex. 2015 ¶ 117. Nor is this limitation inherent because Huang2 does not “necessarily include the unstated limitation.” *Transclean*, 290 F.3d at 1373. That Huang2 does not disclose “calcium” is not dispositive. Indeed, Huang2 does not disclose the experimental protocol by which its collagen was isolated, which may have involved the use of calcium salts or calcium-containing reagents. Ex. 2015 ¶ 117 (citing Ex. 1005, 1792 (Huang2 stating that collagen type I was purchased from Elastin Products, Inc.)).

Moreover, residual calcium exists in electrospun collagen fibers due to many sources, some of which are disclosed by Huang2. Ex. 2015 ¶ 118 (“[R]esidual calcium is necessarily imparted to electrospun fibers from a variety of conventional sources, including compounds utilized in both electrospinning and cell culture.”). Dr. Mikos testifies that residual calcium levels are driven by, among other things, the source of collagen and the presence of chemical cross-linkers, buffer solutions, or cell culture compounds. *Id.*

Huang2’s scaffold necessarily includes residual calcium. For example, the cells seeded onto Huang2’s scaffold are grown in a culture medium including “10% fetal bovine serum.” Ex. 1005, 1792. Dr. Mikos testifies that FBS “naturally contains high concentrations of calcium, which is necessary for growth of the cells seeded on the scaffold.” Ex. 2015 ¶ 119. When collagen scaffolds are placed in a

medium with FBS, the scaffolds will chelate calcium present in the FBS, which *necessarily* increases the residual calcium in the fibers. *Id.* (explaining this is especially so where PCL is present because the carboxyl terminated PCL is deprotonated at physiologic pH and, therefore, is negatively charged, which chelates the positively charged calcium).

Accordingly, a POSITA would understand that Huang2's fibers necessarily include residual calcium. *Id.* ¶ 120. Petitioner has not met its burden to demonstrate that the residual calcium present in Huang2's scaffold is necessarily "less than about 8 wt %," as claimed. Petitioner fails to demonstrate inherency.

**c) Claim 4**

Dependent claim 4 further recites that "the scaffold has an average porosity from about 60% to about 90%." Ex. 1001, 23:14-15. Petitioner contends that Huang2 discloses "high porosity" and that a POSITA would understand this to include the claimed range, which is allegedly supported by Kumbar. Pet. 35; *see infra* § V.C (addressing Kumbar and incorporated herein by reference).

Huang2's generic disclosure of "high porosity" does not expressly anticipate the specifically claimed range. Nor is this limitation inherent because Huang2 does not "necessarily include the unstated limitation." *Transclean*, 290 F.3d at 1373; Ex. 2015 ¶ 122.

As an initial matter, Huang2's vague characterization of electrospun scaffolds

as having “high porosity” does not generally apply to aligned scaffolds. Ex. 1005, 1791 (“[E]lectrospun nanofibrous matrices characterized by ultrafine continuous nanoscale fibers, high surface-to-volume ratio, high porosity and variable pore-size distribution have great potential to mimic the skin ECM.”); Ex. 2015 ¶ 123. In fact, highly aligned fibers, like those Petitioner alleges are disclosed by Huang<sup>2</sup>, typically suffer from relatively *lower* porosity. Pet. 29 (“highly aligned”); Ex. 2015 ¶ 123 (“As compared to randomly arrayed fibers, aligned fibers pack together more tightly leaving smaller spaces between fibers and, therefore, lower porosity.”). This is a known disadvantage of such fibers, as evidenced by Petitioner’s Kuo reference, which states that “a major limitation of aligned scaffolds [is] their low porosity as a result of closely packed aligned fibers.” Ex. 1018 ¶ 112.

Moreover, the specific porosity of aligned electrospun fibers is controlled by many external factors. For example, Dr. Simpson explains that “[t]he properties of the resulting fibrous scaffold depend on several factors” associated with electrospinning, including the polymer’s molecular weight, the solution composition, the flow rate, and others. Ex. 1003 ¶ 32; *see also* Ex. 1006, 4-5 (explaining that an electrospun fiber’s “porosity and pore-size distribution greatly depend[] on the[] parameters selected for electrospinning”).

Dr. Simpson and Dr. Mikos agree that a scaffold’s porosity is dictated by electrospinning parameters like polymer molecular weight and solution properties.

Ex. 2015 ¶ 124 (Dr. Mikos explaining that “the porosity of aligned electrospun fibers is influenced by many factors, including the electrospinning solution, the electrospinning process itself, fiber diameter, extent of alignment, density, and layering.”); Ex. 2017, 42:18-43:4 (Dr. Simpson testifying that “certainly electrospinning conditions affect porosity,” most particularly by “the conditions that produce specific fiber sizes,” i.e., “polymer molecular weight and polymer solution properties”); Ex. 1013, 2 (“[P]ore dimension can be regulated ... by controlling ... the identity, degree of chain entanglements, and concentration of the starting polymer.”).

And, as Dr. Simpson testified, without knowing electrospinning factors like molecular weight and solution composition, the properties of a scaffold—including porosity—*cannot be known* without “measuring or testing” the fibers themselves. Ex. 2017, 53:8-19; Ex. 2015 ¶ 124 (“Without knowing these factors, particularly the electrospinning solution composition, the porosity of a scaffold cannot be known without being specifically measured.”). The Petition does not report any such measurements or tests.

As such, the porosity is not known, and the claimed porosity range is certainly not inherent. A POSITA would have understood that Huang2’s reference to “high porosity” is a relative term where the actual porosity is heavily dependent on various factors that are unexplored in the Petition. Huang2’s porosity does not necessarily

fall within the claimed range. Ex. 2015 ¶ 125.

**C. Ground 2: Huang2 and Kumbar do not render claim 4 obvious**

Alternatively, Petitioner alleges that Kumbar teaches “collagen type I fibers [with] a porosity of 89%,” which decreased to 71% when the fibers were cross-linked. Pet. 45. Petitioner alleges that a POSITA “would have been motivated to look at [Kumbar,] the reference cited by Huang2 in support of the ‘high porosity.’” *Id.* at 44-46.

The arguments made above regarding the lack of anticipation of claim 4 are incorporated herein. *Supra* § V.B.3.c. Moreover, a POSITA would not have expected success in utilizing Kumbar’s porosity in Huang2’s scaffold for several reasons. Ex. 2015 ¶¶ 127-140. First, Kumbar agrees that, as discussed above, electrospinning factors determine a scaffold’s porosity: “porosity and pore-size distribution greatly depend[] on the[] parameters selected for electrospinning,” including “polymer molecular weight” and “polymer solution properties.” Ex. 1006, 4. A POSITA would not expect to achieve Kumbar’s high porosity levels in Huang2’s scaffold given the notably different electrospinning parameters used in each reference. Ex. 2015 ¶¶ 131-135.

Importantly, Huang2 and Kumbar electrospin fibers with *different polymers*: Huang2 discloses a 3:1 blend of PCL and collagen, while Kumbar instead discloses scaffolds made from pure collagen or cross-linked pure collagen. *Compare*

Ex. 1005, 1792, *with* Ex. 1006, 8; Ex. 2015 ¶ 132. In fact, Kumbar does not disclose *any* porosity values for a PCL/collagen blend like that used by Huang2. Ex. 1006, 7-8 (disclosing porosity for collagen, PLAGA, PHBV, and silk fibroin but not a PCL/collagen blend). Because the electrospinning polymers differ, the electrospinning solution properties—and consequently the porosities—of Huang2 and Kumbar also necessarily differ. Ex. 2015 ¶ 133; Ex. 2017, 42:18-43:4 (Dr. Simpson testifying that porosity is most significantly affected by “the conditions that produce specific fiber sizes” including “polymer molecular weight and polymer solution properties”).

For example, the different electrospinning solutions present different viscosities, which directly impact porosity. Ex. 2015 ¶ 134; Ex. 1010, 618 (Dr. Simpson stating that “fiber diameter and pore dimension ... can be largely controlled by regulating the concentration of polymer (viscosity and degree of chain entanglements) present in the starting solution”); Ex. 2017, 51:4-10 (Dr. Simpson explaining that viscosity is the “principal determinant of fiber size”). Indeed, Huang2’s PCL/collagen blend necessarily has a higher viscosity than Kumbar, due to the presence of PCL, which produces larger fiber diameters. Ex. 2015 ¶¶ 134 (“[T]he presence of PCL in Huang2’s PCL/collagen blend increases the solution viscosity because of the chain entanglements formed by PCL. This increased viscosity necessarily produces more uniform fibers without beads. It also produces

fibers with larger fiber diameter.”), 135 (describing lower viscosity of pure collagen solutions); Ex. 2017, 52:6-9 (Dr. Simpson agreeing that “the blend collagen PCL would have a higher viscosity than just the collagen”).

Accordingly, Kumbar’s disclosure of the porosity of pure collagen does not apply to Huang2’s PCL/collagen blend because the electrospinning solution properties that determine porosity, like viscosity, necessarily vary between the solutions. Ex. 2015 ¶ 135 (“[A] POSITA would have understood that Kumbar’s pure collagen electrospinning solution has lower viscosity and, consequently, produces smaller diameter fibers than the blend disclosed by Huang2.”).

Additionally, Huang2’s porosity is necessarily lower than Kumbar’s due to the aligned fibers present in Huang2’s scaffold, which are not present in Kumbar’s cited embodiments. Pet. 45; Ex. 2015 ¶ 139; *compare* Ex. 1005, 1794 (“A majority of the fibers ... aligned in the same direction.”), *with* Ex. 1006, 8 (failing to disclose aligned fibers for the relied-upon embodiments).

Given these differences, a POSITA would not have expected success in modifying Huang2 to reflect Kumbar’s porosities, where Kumbar’s values reflect (1) a non-aligned scaffold that (2) comprises pure collagen. The Petition presents no reason to conclude the claimed porosity levels would have been obvious, let alone successful, in Huang2’s (1) aligned scaffold that (2) comprises a 3:1 PCL/collagen blend. A POSITA would not have expected success in modifying Huang2’s scaffold

to possess the porosity disclosed by Kumbar where Huang<sup>2</sup> does not present electrospinning solution properties that support Kumbar’s porosity levels. Ex. 2015 ¶¶ 138-140. Indeed, as Dr. Simpson testified, without knowing the electrospinning parameters, the resulting properties of the scaffold cannot be known “without measuring or testing them.” Ex. 2017, 538-19.

**D. Ground 3: Lee does not anticipate claims 1-12**

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

Claim 1 recites a “FFT analysis result ... hav[ing] adjacent major peaks with about 180° apart from each other.” Ex. 1001, 23:7-9. Petitioner contends that Lee anticipates. Pet. 47, 49.

The theory upon which Petitioner relies in asserting anticipation by Lee is unclear. As detailed below, *see infra* V.D.2, Petitioner does not identify with particularity *any* basis for alleging express or inherent anticipation. 35 U.S.C. § 312(a)(3); *see also* DI 37 (“Petitioner does not clearly assert in the Petition that the fibers taught by Lee necessarily or inherently satisfy the FFT analysis requirement.... Petitioner’s grounds based on Lee may ultimately fail on the merits due to this lack of specificity.”).

Rather, Petitioner’s contentions turn on whether the prior art would have motivated a POSITA to conduct FFT analysis of Lee’s fibers, Pet. 52-53, which presents a question that the Board found to be beside the point. DI 38 (“[T]he

challenged claims are directed to a scaffold, with the FFT analysis result recited as a *property* of the electrospun collagen fibers used in the scaffold. As such, we do not find it necessary for the prior art to have explicitly taught or motivated a POSITA to conduct an FFT analysis of the aligned fibers taught by Lee.”).

It is Petitioner’s burden to identify its challenges “with particularity” and Petitioner falls short here. *Med-El Elekrtomedizinische Gerate GES.M.B.H v. Sonova AG*, IPR2021-00023, Paper 28 at 21 (PTAB Mar. 2022) (“The purpose of § 312(a) is to ensure Patent Owner is on notice of the allegations forming the basis of the challenges against the subject patent.”); *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2015) (“[T]he petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.”). This cannot be remedied on Reply. CTPG 73.

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

**a) Lee does not expressly disclose this limitation**

First, regarding express anticipation, the Petition does not assert that Lee discloses FFT *at all*, much less the claimed FFT analysis result. Pet. 49; Ex. 1011. Lee cannot expressly disclose the claimed FFT analysis result when FFT is not employed. Ex. 2015 ¶ 143; Ex. 2017, 154:8-10 (“Q. Does Lee disclose using FFT to measure alignment? A. No.”).

**b) Lee does not inherently disclose this limitation**

Second, regarding inherent anticipation, the Petition does not reference “inherency,” “inherent” properties, or “necessarily present” characteristics at all when discussing Lee. Pet. 47-53; Ex. 2015 ¶ 144. As noted in the Decision on Institution, “Petitioner does not clearly assert in the Petition that the fibers taught by Lee necessarily or inherently satisfy the FFT analysis requirement.” DI 37 (“Petitioner’s grounds based on Lee may ultimately fail on the merits due to this lack of specificity.”).

Instead, Petitioner inappositely contends that a POSITA would have known “that a FFT analysis *could be* performed to further confirm alignment,” which “*would show* the fibers were oriented on the scaffold in Lee in an aligned manner.” *Id.* (citing Pet. 52-53). But these contentions regarding what a POSITA could do are insufficient to invoke the strict inherency doctrine, let alone to establish by a preponderance of the evidence that the limitation is inherently (necessarily, inevitably) present. The Petition makes no such allegation.

To the extent the Board were to consider these contentions as pertinent to inherency, these contentions fail.<sup>7</sup> Petitioner fails to show that adjacent major peaks

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<sup>7</sup> The Petition contends that Lee *anticipates*. Accordingly, even if a POSITA would

are necessarily present in Lee's fibers simply because a POSITA *could* run FFT, which Petitioner alleges would show the fibers oriented in an aligned manner. Pet. 52-53. A contention that FFT would show fibers "oriented ... in an aligned manner" is not a contention that Lee's fibers necessarily include the claimed FFT result with "adjacent major peaks with about 180° apart." Pet. 52-53; Ex. 2015 ¶ 145 ("[F]ibers being oriented in an aligned manner is not an element of the claims nor does the Petitioner argue that the claim language would necessarily be present."). Moreover, that Dr. Simpson purports to have run a single FFT analysis is not a contention that the fibers taught by Lee necessarily or inherently satisfy the claimed FFT analysis result. Pet. 53.

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

Any showing of inherency must have been presented in the Petition. *See generally* Pet. 47-53 (citing Ex. 1003 ¶¶ 173-240). It cannot be incorporated by

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have known that alignment could be determined with FFT, that is irrelevant. It has no bearing on whether Lee *inherently discloses* the claimed adjacent major peaks.

reference to Dr. Simpson's declaration. However, *even if* it could be incorporated by reference, the Petition fails to cite any portion of Dr. Simpson's declaration to support an inherency theory regarding Lee. Indeed, the cited portions *also* fail to mention inherency or necessarily present characteristics. Ex. 1003 ¶¶ 173-240.

It is Petitioner who chose to rely upon Lee, and it is Petitioner who chose to assert anticipation. Petitioner was required to file a Petition that "identifies, in writing and *with particularity* ... the grounds on which the challenge to each claim is based, and the evidence that supports the grounds." 35 U.S.C. § 312(a)(3) (emphasis added). It simply failed to do so and may not, on Reply, articulate a new theory of inherency that it did not present in its Petition. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) ("It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify 'with particularity' the 'evidence that supports the grounds for the challenge to each claim.'"); *In re Magnum*, 829 F.3d at 1381 ("[T]he Board must base its decision on arguments that were advanced by a party, and to which the opposing party was given a chance to respond."); CTPG (Nov. 2019) 73 ("Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.").

**c) Dr. Simpson's post-hoc FFT analysis is entitled to no weight**

To support its allegation that Lee anticipates this limitation, Petitioner relies

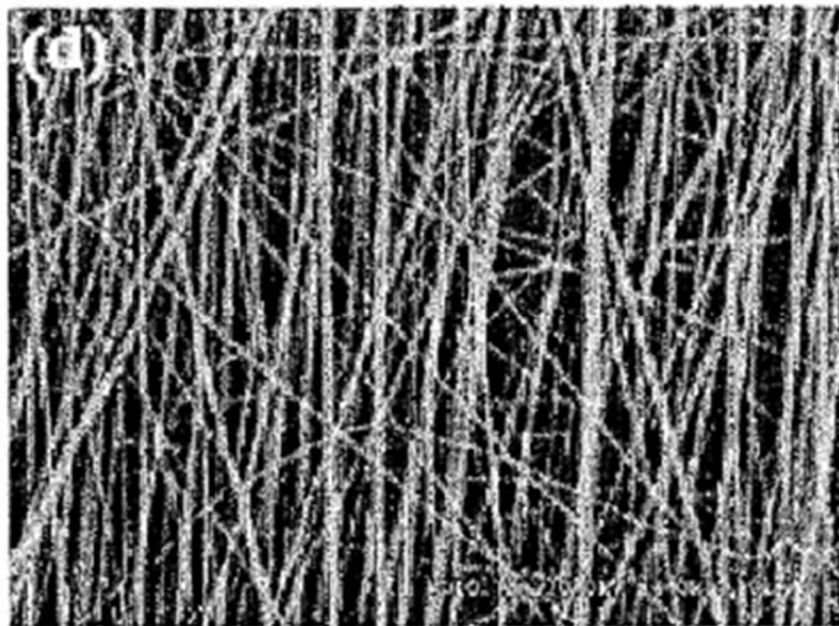
upon Dr. Simpson's post-hoc testing and alleges that this demonstrates "adjacent major peaks" as claimed. But this testing is entitled to no weight for reasons like those discussed above. *Supra* V.B.2.

Dr. Simpson states that he "conducted [his] own analysis of Lee's Figure 1D using the FFT analysis described in the '223 patent." Ex. 1003 ¶ 188. This is incorrect. Dr. Simpson's testing is plainly inconsistent with "the FFT analysis described in the '223 patent." Ex. 2015 ¶ 146.

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

Dr. Mikos testifies that image quality is the single most important factor in FFT analysis. Ex. 2015 ¶ 149; *see also* Ex. 2017, 142:14-15 ("You should always be collecting data with the best capability that you have."). Without a sufficient image, FFT testing results cannot be credited. Ex. 2015 ¶ 149.

Here, however, Dr. Simpson did *not* test high quality images of the type he typically analyzes. *Id.* at 138:23-139:16, 157:8-14. Instead, Dr. Simpson performed FFT analysis on a remarkably poor-quality photocopy of Lee's SEM image, shown below (which did not even come from Lee, but instead from Lee's provisional application).



Ex. 1003 ¶ 184.

Immediately apparent from visual inspection of this image is its poor quality with a facial lack of contrast between individual fibers, especially among fibers toward the background of Lee’s scaffold. Ex. 2015 ¶ 151 (“[A] POSITA would never conduct FFT analysis on such an image.... Absent clear delineation between fibers, especially regarding deeper fibers, the FFT analysis incorrectly analyzes the orientation of the fiber scaffold.”).

Performing FFT analysis on a reproduction of a SEM image like that shown above can lead to invalid and inaccurate results “due to the excessive noise” present in that image. Ex. 2015 ¶ 152. Dr. Simpson himself explained as much, stating that images “composed largely of optical noise,” like that depicted in the Lee provisional image above (*see id.*), are “unsuitable for analysis” with FFT because “individual

fibers are not detected.” Ex. 1010, 605. Dr. Simpson testified that, in the Lee provisional image shown above, he “can see fibers” and “edges.” Ex. 2017, 62:9-16. But, even if some portions of this image contain vaguely discernible fibers and edges, many other portions do not, with just one example shown below.



Ex. 1003 ¶ 184 (taken from the lower right portion of the image reproduced at ¶ 184). As shown above, the edges between individual fibers are entirely lost. As Dr. Mikos testified, “Lee’s image is ‘unsuitable for analysis’ because it contains optical noise that prevents sufficient discernment of the individual fibers and/or edges.” Ex. 2015 ¶ 152. Dr. Simpson fails to reckon with this lack of quality or the extent of “optical noise” this image depicts.

Photocopied images like that used by Dr. Simpson introduce noise, blur, and uneven illumination to the analysis. Ex. 2015 ¶¶ 150, 158. Image contrast is necessarily reduced and fine details—which are essential to a reliable FFT result—are lost. *Id.* ¶ 150; Ex. 1010, 609 (Dr. Simpson acknowledging that uneven illumination introduces error). Dr. Mikos testifies that noise and artifacts introduced by testing reproduced images adversely affects FFT plot shape with high frequency features, which reflect fiber orientation, most affected. Ex. 2015 ¶ 150; *see, e.g.*, Ex. 1010, 612 (Dr. Simpson acknowledging that noise introduces artifacts into the

FFT result).

In fact, both Dr. Mikos and Dr. Simpson testified that they do not normally perform FFT analysis with reproduced or photocopied images for these reasons. Ex. 2015 ¶¶ 93, 152; Ex. 2017, 157:8-14 (“Q. Do you normally perform FFT analysis with a photocopied image? ... A. No.”), 157:23-158:3 (Dr. Simpson testifying that he does not advise his students to use photocopied images for FFT analysis).

## **(2) Lee’s image was tested differently**

Despite stating that he “us[ed] the FFT analysis described in the ’223 patent,” Ex. 1003 ¶ 188, Dr. Simpson did not. As an initial matter, Dr. Simpson’s declaration is apparently incomplete and omits important details about the FFT analysis that Dr. Simpson performed. In fact, despite the declaration’s silence on this point, Dr. Simpson apparently applied a mask to Lee’s image but failed to disclose that in his declaration. *Compare* Ex. 1003 ¶ 110 (depicting a mask applied to Huang2’s image), *with id.* ¶ 184 (*not* depicting a mask applied to Lee’s image); Ex. 2017, 162:9-10 (“[I p]ut a mask on it, processed the FFT.”), 163:11-15 (“Q. Where in your report do you discuss applying a mask to Lee? A. I’m sure it’s -- I would have thought it was here but it’s not.”).

This is doubly problematic. First, without documenting where or how Dr. Simpson applied a mask, his FFT analysis cannot be evaluated. As discussed in

his past paper, it is important that FFT analysis occur over “as large as an area as possible” to avoid “bias[ing] the 2D FFT process.” Ex. 1010, 606. But the declaration lacks any discussion of how the mask was applied and, accordingly, it is unclear how much of Lee’s image was discarded when Dr. Simpson applied a mask. Ex. 2015 ¶ 155.

Second, application of a mask is not “the FFT analysis described in the ’223 patent.” Ex. 1003 ¶ 188. Specifically, the ’223 patent incorporates the FFT analysis described in Dr. Simpson’s 2008 paper (Ex. 1010), but this paper discloses only an *optional* mask—an option that was not exercised in the ’223 patent. Ex. 1001, Fig. 8A (depicting the tested image without a mask); Ex. 2015 ¶ 155.

As discussed above, inclusion or exclusion of a mask *directly* impacts the resulting FFT plot, as Dr. Simpson’s 2008 paper explains. As reported there, when performing FFT analysis on fibers oriented at 45°, the FFT plot included “edge noise” that appeared as small peaks in the FFT plot. Ex. 1010, 615. In particular, “[t]he unmasked image produces a 2D FFT alignment plot with artifacts in the guise of small peaks on either side of the alignment peaks (Fig. 3N, arrows). Processing the image with a window mask removes this spurious information without altering the height of the alignment peaks.” *Id.* In other words, inclusion or exclusion of a mask is not a trivial detail. Ex. 2015 ¶ 156. Adding or omitting a mask impacts the resulting FFT plot and results in different peaks being included. *Id.*; Ex. 1010, 615.

In sum, despite his statement to the contrary, Dr. Simpson did *not* perform the FFT analysis described in the '223 patent and, in doing so, also violated his own past statements regarding the importance of testing a sufficiently representative sample.

### **(3) Conclusion**

It is Petitioner who chose to rely upon Lee, and it is Petitioner who chose to assert anticipation despite Lee's failure to disclose FFT. Petitioner now bears the burden of proving anticipation by a preponderance of evidence. It cannot meet that burden by relying on post hoc testing of a poor quality, photocopied image that violates Dr. Simpson's own past statements about the image quality necessary for FFT analysis. Here, the tested image consists largely of optical noise and is "unsuitable for analysis" with FFT because "individual fibers are not detected." Ex. 1010, 605. Dr. Simpson's current claim that Lee's image is sufficient for such testing is simply not credible. *See Wilson v. Martin*, 789 F. App'x 861, 870 (Fed. Cir. 2019) ("The purpose of extrinsic evidence in an anticipation analysis 'is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, *not to fill gaps in the reference.*'") (emphasis added); *Turlay*, 304 F.2d at 899 ("It is well established that an anticipation rejection cannot be predicated on an ambiguous reference.").

#### **d) The FFT protocol is insufficiently explained**

With this background of omission and inconsistency, Dr. Simpson's bare

statement that he “conducted [his] own analysis on Lee’s Figure 1D using the FFT analysis described in the ’223 patent” is insufficient to satisfy 37 C.F.R. § 42.65(b). *Luitpold Pharms.*, IPR2018-01640, Paper 19 at 23-24 (finding insufficient an expert declaration that “fails to provide any specificity as to the steps taken”).

As discussed above, a POSITA typically documents the steps taken in performing an FFT analysis. Ex. 2017, 59:19-60:8. Dr. Simpson’s declaration, however, does not even identify something as critical as the presence of a mask applied to the tested image. *Id.* at 163:11-15. Nor does Dr. Simpson recall the *version of software* he used to conduct his analysis, let alone the parameters he applied in testing a flawed photocopied of Lee’s image. *Id.* at 140:24-141:4; Ex. 2015 ¶ 160. Likewise, Dr. Simpson did not document where or how he applied the circular projection in the ImageJ software to his FFT output image to generate his FFT plot, a “critical” aspect of FFT analysis. Ex. 2015 ¶ 159 (“If the circular selection does not capture a representative portion of the FFT output image, it will bias the results.”). In this vacuum, reproducing his testing is impossible.

In addition to the inconsistencies discussed above, Dr. Simpson’s earlier paper, incorporated by reference into the ’223 patent, describes other critical aspects of FFT analysis that are essential, but are not accounted for in Dr. Simpson’s testing, and which *directly impact* both the validity of FFT testing and the shape of the resultant FFT plot. Ex. 2015 ¶¶157-161. For example, Dr. Simpson’s earlier paper

emphasizes the importance of image quality to reliable FFT testing. In his 2008 paper, Dr. Simpson utilized images that were “stored and analyzed as uncompressed .TIF files to preserve image integrity [because] the image compression used in .JPG format will degrade image integrity.” Ex. 1010, 607; Ex. 2017, 142:14-15 (“You should always be collecting data with the best capability that you have.”). In his post-hoc testing, however, Dr. Simpson “ha[d] no idea” how Lee’s image was stored and did not attempt to account for that in his analysis. Ex. 2017, 160:23-161:2.

Again, it was Petitioner’s burden to demonstrate anticipation; that burden cannot be satisfied with incomplete post-hoc testing that violates 37 C.F.R. § 42.65(b). Dr. Simpson’s results cannot be credited. For these reasons, Lee does not anticipate independent claim 1.

### **3. Lee does not anticipate dependent claims 2-12**

Dependent claims 2-12 include all limitations of independent claim 1 and, for the same reasons articulated above, Petitioner’s contentions likewise fail.

#### **a) Claim 2**

Dependent claim 2 further recites that “the fibers comprise type I collagen in its native triple helical structure.” Ex. 1001, 23:10-11. Petitioner contends Lee uses type I collagen, which was known to have a triple-helical form, lest it would have been called gelatin. Pet. 54.

As in Ground 1, which arguments are incorporated herein, Lee is silent as to

the form of collagen in its fibers and, therefore, does not expressly anticipate. Ex. 2015 ¶ 163; *supra* § V.B.3.a. Nor is this limitation inherent. *Transclean*, 290 F.3d at 1373. A POSITA would have understood that, given Lee’s disclosed electrospinning and cell culture processes, its fibers do *not* necessarily possess collagen in its native triple helical structure. Ex. 2015 ¶¶ 164-167.

More specifically and like Huang<sup>2</sup>, Lee also utilizes PCL, HFIP, and fetal bovine serum in its electrospinning and cell culture processes. Ex. 1011 ¶¶ 62-63, 69. As Dr. Mikos explains, these components necessarily denature Lee’s collagen out of its native triple helical structure. Ex. 2015 ¶¶ 165 (explaining that degradation of PCL, accelerated by the presence of fetal bovine serum, releases acidic byproducts that disrupt the bonds that keep collagen in its triple helical form); 166 (explaining that HFIP was known to denature collagen); *see also* Ex. 2019, Abstract (“[T]he very properties that have established collagen as the leading natural biomaterial are lost when it is electro-spun into nano-fibres out of fluoroalcohols such as [HFIP].”), 2308 (“Electro-spinning collagen out of fluoroalcohols denatures collagen to gelatin.”).

Accordingly, a POSITA would have known that the type I collagen used in Lee would have denatured such that the resulting fibers would not necessarily comprise collagen in its native triple helical structure. Ex. 2015 ¶ 167. Petitioner fails to meet its burden to demonstrate inherency.

**b) Claim 3**

Dependent claim 3 further recites that “the fiber has less than about 8 wt % residual calcium.” Ex. 1001, 23:12-13. Petitioner contends that Lee “does not require or disclose using calcium or calcium-containing compounds” and, therefore, “necessarily ha[s] less than about 8 wt % residual calcium.” Pet. 55.

Lee is silent regarding residual calcium and, therefore, does not expressly anticipate. Ex. 1011; Ex. 2015 ¶ 169. Nor does Lee inherently anticipate because it does not “necessarily include the unstated limitation.” *Transclean*, 290 F.3d at 1373. As above regarding Ground 1, which arguments are incorporated herein, it is not dispositive that Lee does not disclose “calcium.” Ex. 2015 ¶ 170 (explaining the protocol for isolating Lee’s collagen may involve calcium salts or reagents); Pet. 55.

Residual calcium is present in electrospun collagen fibers from many sources including the source of collagen and the presence of chemical cross-linkers, buffer solutions, or cell culture compounds. Ex. 2015 ¶ 171. As above regarding Huang2, Lee’s cells are also cultured in a medium “with a high amount of serum (e.g., 4.5%-20% fetal bovine serum (FBS)).” Ex. 1011 ¶ 37. As Dr. Mikos testified, Lee’s scaffolds will chelate calcium present in the fetal bovine serum, which necessarily increases the residual calcium in the fibers. Ex. 2015 ¶ 172; *supra* § V.B.3.b.

Moreover, Lee’s scaffold is cross-linked with glutaraldehyde solution. Ex. 1011 ¶ 63. As Dr. Simpson explained, glutaraldehyde is “implicated in the

development of calcification.” Ex. 2020, 1594. In fact, Dr. Mikos testifies that glutaraldehyde-crosslinked fibers, like Lee’s, mineralize more effectively than non-crosslinked fibers because crosslinking enhances collagen’s mechanical stability, which is crucial for mineralization and calcification. Ex. 2015 ¶ 173. This stands in stark contrast with the claimed scaffold, which seeks to *minimize* calcium to less than 8 wt %. Ex. 1001, 23:12-13.

Accordingly, a POSITA would understand that Huang’s fibers necessarily include residual calcium. Ex. 2015 ¶ 174. Petitioner has not met its burden to demonstrate that Huang2’s scaffold necessarily includes “less than about 8 wt %,” as claimed. Petitioner fails to demonstrate inherency.

**c) Claim 4**

Dependent claim 4 further recites that “the scaffold has an average porosity from about 60% to about 90%.” Ex. 1001, 23:14-15. Petitioner contends that Lee discloses “high porosity.” Pet. 55-56. According to Petitioner, a POSITA would view this generic disclosure as anticipating the claimed range, which is allegedly supported by prior art to Mikos.<sup>8</sup> Pet. 56.

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<sup>8</sup> The first-named inventor on the cited Mikos patent is Antonios G. Mikos, Patent Owner’s declarant. Ex. 2017, 196:19-23 (stating that this patent would be a reliable

Petitioner’s reliance on Lee’s general disclosure of “high porosity” in “some embodiments,” Ex. 1011 ¶ 55, is insufficient to expressly anticipate the specifically claimed range or to demonstrate that Lee inherently includes a porosity within that range. As discussed above and incorporated herein, *supra* §§ V.B.3.c, V.C, a POSITA would have known that many factors impact a scaffold’s porosity including, e.g., its fiber diameter, its alignment, and the electrospinning process itself. Ex. 2015 ¶¶ 177-178; Ex. 1006, 4-5 (explaining that “porosity and pore-size distribution greatly depend[] on the[] parameters selected for electrospinning”); Ex. 1003 ¶ 32. For example, aligned fibers typically suffer from lower porosity because the fibers are packed together, leaving smaller spaces between fibers and, therefore, lower porosity. Ex. 2015 ¶ 177; Ex. 1018 ¶ 112 (identifying “low porosity as a result of closely packed aligned fibers”).

A POSITA would have understood Lee’s reference to “high porosity” as a characteristic of “some embodiments” of electrospun scaffolds to be a relative term where the actual porosity is heavily dependent on various factors that are unexplored in the Petition. Lee’s porosity does not necessarily fall within the claimed range.

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source of information for a POSITA, “[e]specially coming from [Dr. Mikos’s] laboratory”).

Ex. 2015 ¶ 179 (explaining that the increased viscosity imparted to Lee’s electrospinning solution due to the presence of PCL leads to larger fiber diameters); Ex. 1011 ¶ 55. Dr. Simpson confirmed as much, stating that without knowing the electrospinning parameters, the resulting properties of the scaffold cannot be known “without measuring or testing them.” Ex. 2017, 538-19.

Reliance on Dr. Mikos’ cited patent is misplaced. Ex. 2015 ¶¶ 181-182. As Dr. Mikos testifies, his patent teaches a salt leaching process used to impact porosity in a cartilage or bone implant; it does not apply to Lee’s muscle tissue scaffold. Ex. 1014, 2:45-49; Ex. 2015 ¶ 183 (explaining that the appropriate porosity for cartilage or bone scaffolds varies greatly from that of Lee’s muscle scaffold). Moreover, Dr. Mikos’s patent teaches various polymers used for such implants but does not discuss collagen/PCL scaffolds like Lee’s. Ex. 1014, 3:7-10, 5:14-17; Ex. 2015 ¶ 183. Finally, Dr. Mikos’s salt leaching technique individually varies both porosity *and* pore size, which is not possible through electrospinning as taught by Lee. Ex. 2015 ¶ 183.

Accordingly, a POSITA would not have found the claimed porosity range to be inherently disclosed by Lee.

#### **d) Claim 12**

Claim 12 depends on claim 11, which depends on claim 1. Dependent claim 11 recites “A method of cell culture comprising culturing cells on the scaffold

according to claim 1....” and dependent claim 12 further limits “the cells” recited in claim 11 as “selected from the group consisting of stem cells ....” Ex. 1001, 24:21-27. Petitioner relies on Lee’s teachings that “[s]keletal muscle cells may be provided by ... differentiating stem or progenitor cells” and that “[s]keletal muscle cells include ... myoblasts,” which are described as “a type of muscle stem cell” in Lee. Pet. 63-64 (citing Ex. 1011 ¶¶ 30, 40).

Petitioner misapprehends Lee. Stem cells are a specific type of cell that is capable of self-replicating and differentiating into different cell types. Ex. 2015 ¶ 186; Ex. 2004, 315 (defining stem cells as having “the capacity for both replication and differentiation, and has pluripotentiality”); Ex. 1001, 1:19-23 (explaining that stem cells can differentiate “into osteoblasts, chondrocytes, ligament or tendon”).

By contrast, the only cells cultured on Lee’s scaffolds are human skeletal muscle cells (“hSkMCs”). Ex. 1011 ¶¶ 69, 72. hSkMCs are fully differentiated muscle cells; they are not capable of further differentiating into different cell types. *Id.* ¶ 188. Instead, they always remain as muscle cells. *Id.* Lee’s teaching that its hSkMCs may be *obtained* in different ways, e.g., by isolating cells from harvested tissue or by differentiating stem or progenitor cells, Ex. 1011, ¶ 40, speaks to how Lee *obtained* its hSkMCs; it does not change the fact that the hSkMCs themselves are fully differentiated muscle cells, not stem cells. Ex. 2015 ¶ 187.

Petitioner’s reliance on Lee’s inaccurate description of a myoblast as “a type

of muscle stem cell” is misguided. Ex. 1011 ¶ 30. Myoblasts are not stem cells. Ex. 2015 ¶ 188. As Lee clearly explains, “myoblasts are capable of dividing and repopulating” to repair injured myofibers. Ex. 1011 ¶ 30. Myoblasts, however, are *not* stem cells because they cannot differentiate into different cell *types*; they remain muscle cells. Ex. 2015 ¶ 188 (“[T]hey always remain as muscle cells and are referred to as muscle progenitor cells. Although myoblasts may fuse with other myoblasts to form myotubes, that fusion does not produce a different cell type.”).

Petitioner fails to demonstrate anticipation.

**E. Ground 4: Lee does not render claims 1-12 obvious**

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

As an alternative to Ground 3, Petitioner alleges that Lee renders obvious the claimed “FFT analysis result ... hav[ing] adjacent major peaks with about 180° apart from each other.” Pet. 64-65. Specifically, the Petition alleges that FFT “could be run on Lee’s SEM images to confirm the degree of alignment,” and that a POSITA would have been motivated to do so. *Id.* (citing Ex. 1003 ¶¶ 242-243).

In its Decision on Institution, however, the Board preliminarily determined that these contentions are beside the point. DI 38 (“[T]he challenged claims are directed to a scaffold, with the FFT analysis result recited as a *property* of the electrospun collagen fibers .... [W]e do not find it necessary for the prior art to have

explicitly taught or motivated a POSITA to conduct an FFT analysis of the aligned fibers taught by Lee.”).

Apart from the very allegations the Board found irrelevant, the Petition makes *no additional showing* to demonstrate obviousness over Lee. Pet. 64-66. For example, Petitioner’s contention that POSITA would have been motivated to “run an FFT,” Pet. 64-65, goes only toward a question that the Board indicated is not relevant. Moreover, the contention that a POSITA “would have more than a reasonable expectation of success” also concerns that same irrelevant question of whether a POSITA would have found it obvious to modify Lee’s disclosure. *Id.* at 65-66.

## **2. The Petition does not demonstrate obviousness**

Nonetheless, even if the Board were to consider Petitioner’s contentions regarding whether a POSITA would have been motivated to conduct a FFT analysis, those arguments also fail.

Specifically, Petitioner fails to satisfy its burden to demonstrate a motivation to modify Lee. Petitioner acknowledges that Lee already confirms fiber alignment through three different mechanisms: (1) scanning electron microscopy (SEM) examination, (2) ImageTool 3.0 freeware analysis, and (3) tensile testing. Pet. 49-

52 (SEM and ImageTool), 53 (tensile testing); *see also id.* at 65.<sup>9</sup> Petitioner fails to explain why a POSITA would have been motivated to confirm alignment through FFT—a fourth confirmation mechanism—when alignment has been confirmed already in three different ways. *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) (“[A] petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness.”).

For example, Petitioner does not show that a fourth confirmation mechanism

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<sup>9</sup> Petitioner also argues that a POSITA would have known that a FFT analysis “could be run on Lee’s SEM images to confirm the degree of alignment.” Pet. 65. But this is irrelevant. “Could have” is not the test for obviousness; a credible reason to modify must be shown. *See Belden, Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (“Obviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.”); *Virtek Vision Int’l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 888 (Fed. Cir. 2024) (“It does not suffice to simply be known. A reason for combining must exist.”).

based on FFT would have been needed, expected, or typical in the art. Nor does Petitioner identify any deficiency in the first (SEM examination), second (ImageTool 3.0 analysis), or third mechanisms (tensile testing) by which Lee already confirmed alignment. Petitioner also does not contend that FFT analysis would have imparted some additional or unique benefit over the three mechanisms that Lee already employed. The prima facie case of obviousness must have been made in the Petition; it cannot be made on reply. CTPG 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”).

And in fact, a POSITA would not have done so. As Dr. Mikos testifies, where alignment has already been thoroughly confirmed, as in Lee, a POSITA would see no reason to expend time or money to further reiterate that finding. Ex. 2015 ¶ 190. Moreover, Dr. Simpson testified that performing FFT on SEM images like Lee’s has known “disadvantages,” including that “it’s destructive.” Ex. 2017, 73:2-7. The Petition simply fails to establish that a POSITA would have undertaken FFT testing to reconfirm what was already established, especially in the face of increased cost and time. *See, e.g., Edwards Lifesciences Corp. v. Aortic Innovations LLC*, IPR2023-01232, Paper 10 at 36-37 (PTAB Feb. 7, 2024) (finding the purported motivation to be “inchoate” and “unpersuasive” because the “benefits” of the combination “are already conferred”); *see also UiPath, Inc. v. Rule 14 LLC*,

IPR2024-01304, Paper 8 at 26-27 (PTAB Mar. 14, 2025) (finding no motivation to combine where the primary reference “already includes the option for the user to manually select a data source from a plurality of data sources” and petitioner and its expert offered only conclusory argument in support of its proposed combination); *AMP Plus, Inc. v. DMF, Inc.*, 131 F. 4th 1320, 1325 (Fed. Cir. 2025) (“[T]he law of obviousness does not require the court, or the Board, to develop arguments for a limitation that the petition simply did not make.”).

Finally, Petitioner relies upon Dr. Simpson’s post-hoc testing to support its contention that a POSITA would have expected success in applying a FFT analysis to Lee. Pet. 65-66; Ex. 1003 ¶ 243 (“[A] POSA would have more than a reasonable expectation of success of successfully running an FFT on Lee’s SEM images. Indeed, I was able to run such an analysis.”). However, the obviousness inquiry concerns the time of invention, not the time an expert declaration is prepared. As such, Dr. Simpson does not establish that a POSITA at the time of invention would have expected success. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 974 (Fed. Cir. 2014) (“Obviousness, and expectation of success, are evaluated from the perspective of a person having ordinary skill in the art *at the time of invention.*”) (emphasis added)).

It was Petitioner’s statutory burden to set forth its prima facie case of obviousness in the Petition itself. *See* 35 U.S.C. § 312(a)(3). Petitioner may not

advance a new theory of obviousness on Reply, CTPG 73, nor may the Board decide an obviousness case that was not presented in the Petition itself. *AMP Plus*, 131 F. 4th at 1325.

Accordingly, Petitioner has not demonstrated that Lee renders obvious this limitation or claim 1.

## **VI. CONCLUSION**

Patent Owner respectfully maintains that Petitioner has not met its burden to prevail on any of claims 1-12 in this *inter partes* review.

Dated: October 29, 2025

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

I hereby certify that this response, excluding its table of contents, table of authorities, certification under 37 C.F.R. § 42.24(d), certificate of service, appendix of exhibits has 13,507 words as counted by Microsoft Word, the word-processing system used to prepare this response.

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**Certification of Service**

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

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