

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.,  
Petitioners

v.

LIFENET HEALTH,  
Patent Owner.

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

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**PETITION FOR *INTER PARTES* REVIEW OF  
U.S. PATENT NO. 11,318,227  
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§42.100 *et seq.***

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| B. Lee et al., U.S. Patent Application No. US 2010/0331980 A1,<br>Pub. Date December 1, 2011 .....                                                                                                                                                                                 | 23          |
| C. Huang et al., The Involvement of Integrin $\beta$ 1 Signaling in the<br>Migration and Myofibroblastic Differentiation of Skin Fibroblasts<br>on Anisotropic Collagen-Containing Nanofibers, Biomaterials 33<br>(2012) 1791-1800, available online 2 December 2011 (“Huang2”) 25 | 25          |

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## **PETITIONERS' EXHIBIT LIST**

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                                                                                                                                        |
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| <b>1001</b>        | U.S. Patent No. 11,318,227 to Francis et al. ("the '227 patent")                                                                                                                                                                                                                          |
| <b>1002</b>        | '227 Patent Prosecution History                                                                                                                                                                                                                                                           |
| <b>1003</b>        | Declaration of David G. Simpson, Ph.D.                                                                                                                                                                                                                                                    |
| <b>1004</b>        | CV of David G. Simpson, Ph.D.                                                                                                                                                                                                                                                             |
| <b>1005</b>        | Huang et al., <i>The involvement of integrin <math>\beta 1</math> signaling in the migration and myofibroblastic differentiation of skin fibroblasts on anisotropic collagen-containing nanofibers</i> , 33 Biomaterials 1791-1800 (Feb. 2012) ("Huang2") (available online Dec. 2, 2011) |
| <b>1006</b>        | Kumbar et al., <i>Electrospun nanofiber scaffolds: engineering soft tissues</i> , Biomed. Mater. 3 (2008) ("Kumbar")                                                                                                                                                                      |
| <b>1007</b>        | U.S. Patent No. 10,137,223 Prosecution History                                                                                                                                                                                                                                            |
| <b>1008</b>        | Huang et al., <i>Electrospun collagen-chitosan-TPU nanofibrous scaffolds for tissue engineered tubular grafts</i> , 82 Colloids and Surfaces B: Biointerfaces 307-315 (2011) ("Huang1")                                                                                                   |
| <b>1009</b>        | U.S. Patent App. Pub. No. 2004/0037813 to Simpson et al. ("Simpson")                                                                                                                                                                                                                      |
| <b>1010</b>        | Ayres et al., <i>Measuring fiber alignment in electrospun scaffolds: a user's guide to the 2D fast Fourier transform approach</i> , 19 J. Biomater. Sci. Polymer. 603-621 (2008) ("Ayres 2008")                                                                                           |
| <b>1011</b>        | Lee et al., U.S. Patent Application No. US 2010/0331980 A1, Pub. Date December 1, 2011 ("Lee")                                                                                                                                                                                            |
| <b>1012</b>        | Reserved                                                                                                                                                                                                                                                                                  |
| <b>1013</b>        | Ayres et al., <i>Modulation of Anisotropy in Electrospun Tissue-Engineering Scaffolds: Analysis of Fiber Alignment by the Fast Fourier Transform</i> , 27(32) Biomaterials 5524-5534 (2006) ("Ayres 2006")                                                                                |
| <b>1014</b>        | Reserved                                                                                                                                                                                                                                                                                  |

|             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>1015</b> | Jose et al, <i>Fabrication and Characterization of Aligned Nanofibrous PLGA/Collagen Blends as Bone Tissue Scaffolds</i> , 50 Polymer 3778-85 (2009) (“Jose”)                                                                                                                                                                                                                                                                                                                                              |
| <b>1016</b> | Fu et al, <i>Spatial Arrangement of Polycaprolactone/Collagen Nanofiber Scaffolds Regulates the Wound Healing Related Behaviors of Human Adipose Stromal Cells</i> , 18(5) Tissue Engineering, 631-42 (2012) (“Fu”)                                                                                                                                                                                                                                                                                        |
| <b>1017</b> | Reserved                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>1018</b> | Kuo et al., U.S. Patent Application No. US 2011/0293685 A1, Pub. Date Dec. 1, 2011 (“Kuo”)                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>1019</b> | Beachley et al, <i>Highly Aligned Polymer Nanofiber Structures: Fabrication and Applications in Tissue Engineering</i> (2011) in Vol. 246 Biomedical Applications of Polymeric Nanofibers (Jayakumar & Nair eds. 2011)                                                                                                                                                                                                                                                                                     |
| <b>1020</b> | Declaration of Emma Xu                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>1021</b> | U.S. Provisional Patent App. No. 61/0255,35 (“Lee Provisional”)                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>1022</b> | McClure et al, <i>Tri-Layered Vascular Grafts Composed of Polycaprolactone, Elastin, Collagen, and Silk: Optimization of Graft Properties</i> , 10 J. Mechanical Behavior Biomedical Materials 48 (2012)                                                                                                                                                                                                                                                                                                   |
| <b>1023</b> | Meinel et al., <i>Engineering Cartilage-Like Tissue Using Human Mesenchymal Stem Cells and Silk Protein Scaffolds</i> , 88(3) Biotechnology Bioengineering 379 (2004)                                                                                                                                                                                                                                                                                                                                      |
| <b>1024</b> | June 21, 2022 Memo From Katherine Vidal on Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation (June 21, 2022), available at <a href="https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_.pdf">https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_.pdf</a> |

## **I. INTRODUCTION**

Embody, Inc. and Zimmer Biomet Holdings, Inc. (“Petitioners”) request review of claims 1-8 of U.S. Patent No. 11,318,227 (“the ’227 patent”), which issued on May 3, 2022 and is assigned to LifeNet Health (“Patent Owner”). The ’227 is a divisional application of U.S. Application No. 14/776,106, which issued as U.S. Patent No. 10,137,223 (“the ’223 patent” or the “parent application”).<sup>1</sup>

Claim 1 of the divisional ’227 patent, and its corresponding dependent claims (2-6), rely as its alleged point of novelty a scaffold, containing aligned collagen fibers with peaks 180° apart when measured using a fast Fourier transform or “FFT” analysis. However, prior art *not* before the Examiner during prosecution of the parent ’223 patent or the divisional ’227 patent show a scaffold with collagen containing fibers that are in alignment with the requisite peaks as shown by FFT analysis.

Further, the additional elements recited in claim 1 of the ’227 patent do not distinguish the claimed subject matter from the prior art. For example, claim 1 recites using this non-novel scaffold to treat a tendon, ligament, or nerve injury. Yet, a well-known use of scaffolds with electrospun fibers including collagen is to

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<sup>1</sup> Petitioners have also filed a petition for inter partes review requesting review of claims 1-12 of the parent ’223 patent.

treat a tissue defect, and it was extensively taught in the prior art to use such scaffolds to treat tendon, ligament, or nerve injuries. Likewise, claim 1 also requires that the collagen fibers are “cross-linked.” Yet, chemically crosslinking collagen fibers was also well-known in the prior art and constitutes a routine method to increase the stability and structural integrity of the scaffold, especially when using collagen as a material. Accordingly, claims 1-6 are obvious under 35 U.S.C. § 103 in view of the prior art not before the Examiner during prosecution.

Independent claim 7 (and its dependent claim 8) merely recite methods of culturing cells on the non-novel scaffold containing the aligned fibers with peaks 180° apart as measured by FFT. Such methods, however, were also well-known in the prior art and routinely used to culture cells. Indeed, the '227 patent does not suggest that such methods are anything other than conventional. Accordingly, as set forth in more detail below, inter partes review of claims 1-8 is warranted.

## **II. MANDATORY NOTICES**

**REAL PARTY-IN-INTEREST:** The real party-in-interest (RPI) is Petitioner Embody, Inc. Zimmer Biomet Holdings, Inc. (or “ZBH”) is listed as a party in the related district court litigation discussed below, where LifeNet Health has served a complaint alleging patent infringement against Embody, Inc. and ZBH. ZBH, however, filed a motion to dismiss for lack of personal jurisdiction and venue, which was granted by the district court on September 25, 2024. (Docket No. 39.)

Out on an abundance of caution, Petitioner further identifies ZBH as a real party-in-interest.

**RELATED MATTERS:** The '227 patent is the subject of the following civil action: *LifeNet Health v. Embody, Inc. and Zimmer Biomet Holdings, Inc.*, Case No. 2:23-cv-00479 (E.D. Va.), where the complaint was served on Petitioner Embody on December 4, 2023. (“Related Matter”). Zimmer Biomet Holdings, Inc., filed a motion to dismiss for lack of personal jurisdiction and venue, which as mentioned above, was granted on September 25, 2024. (Docket No. 39.)

**COUNSEL AND SERVICE INFORMATION:**

Petitioners provide the following designation of Lead and Back-Up Counsel.

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
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**III. GROUNDS FOR STANDING**

The '227 patent is available for inter partes review, and the Petitioners are not barred or estopped from requesting inter partes review challenging the patent claims on the grounds identified in this Petition.

**IV. IDENTIFICATION OF CHALLENGE:**

Petitioners identify three grounds of unpatentability:

| Ground | References            | Claims | Basis |
|--------|-----------------------|--------|-------|
| 1.     | Huang2 in view of Kuo | 1-6    | § 103 |
| 2.     | Lee in view of Kuo    | 1-6    | § 103 |
| 3.     | Huang2                | 7-8    | § 102 |

**V. TECHNICAL BACKGROUND**

**A. Electrospinning was a Proven Technique for Producing Nanofibers for use in Treating a Tissue Defect**

Electrospinning was a well-established method for producing nanofibers as of March 14, 2013, the earliest priority date alleged for the '227 patent. (*See* EX1006, 1-2; EX1003, §§III.A-B.) It was—and is—valued for its reproducibility and scalability. (EX1006, 1-2; EX1003, ¶30.) The method uses a high electric

potential to push a charged polymer solution out of a syringe. (*Id.*) The polymer solution is ejected as a jet towards a grounded collector. (EX1006, 1-2; EX1003, ¶31.) As the jet of solvent and polymer is ejected from the syringe and travels towards the collecting target, the solvent evaporates. The polymer molecules form a continuous fiber and are deposited on the grounded collector as a fibrous polymer scaffold. (EX1009, [0156]; EX1006, 1-2; EX1003, ¶31.) Many different parameters, such as the type of polymer and collector used, can alter the fibrous polymer scaffold's properties. (EX1006, 3-5; EX1013, 1; EX1003, ¶32.) For example, it was well-known that aligned fibers could be obtained using a rotating collector, among other methods. (EX1006, 3; EX1005, 1792; EX1009, [0176]; EX1003, ¶32.)

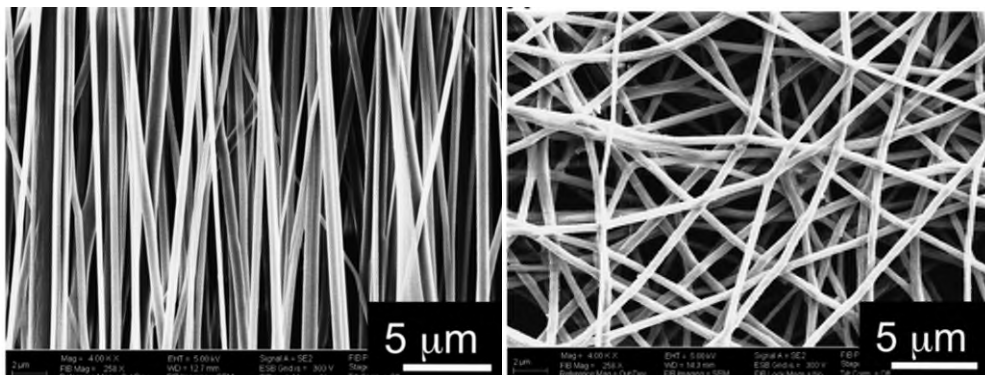
Electrospun nanofiber scaffolds share several key characteristics with the natural extracellular matrix ("ECM") found in the body. (EX1006, 1; EX1008, 308; EX1003, ¶¶33-34.) These features—such as ultrafine continuous fibers, a high surface-to-volume ratio, high porosity, and variable size distribution—make electrospun scaffolds well-suited for use as implantable scaffolds to treat a tissue defect. (EX1008, 308; EX1006, 6, 12; EX1003, ¶¶33-34.) Thus, by March 2013, electrospun scaffolds had been successfully applied in the development of grafts for a variety of tissues, including:

- Skin (EX1005, 1791; EX1006, 7-8; EX1003, ¶35);

- Tendon (EX1018, [0112]; EX1006, 10; EX1003, ¶35);
- Blood vessels (EX1006, 8-10; EX1003, ¶35);
- Muscle (EX1006, 11; EX1003, ¶35);
- Ligament (EX1018, [0112]; EX1003, ¶35); and
- Nerves (EX1006, 10-11; EX1003, ¶35).

**B. Enhancing Biological Performance of Microfiber Scaffolds Through Fiber Alignment and Collagen Incorporation**

As mentioned above, the fibers obtained from electrospinning can either be aligned or randomly oriented in a scaffold as shown in the following images obtained from a scanning electron microscope:



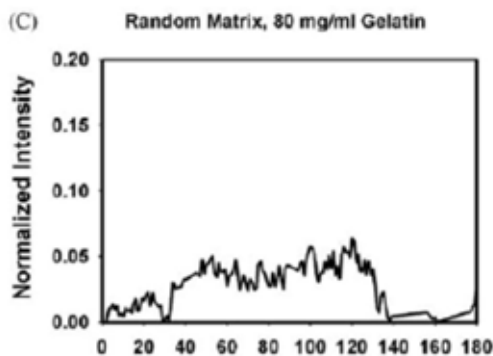
(EX1005, 1793; EX1003, ¶¶38-45.) The photograph on the left shows fibers that are aligned, while the photograph on the right shows fibers that are randomly oriented. Fiber alignment was well-known in the prior art to enhance the mechanical and biological properties of scaffolds. (EX1010, 604; EX1006, 6; EX1018, [0112]; EX1003, ¶¶36-38.) Aligning fibers in nanofiber scaffolds was known to enhance cell proliferation, which is an important quality for creating scaffolds for repairing a tissue defect. (EX1006, 6-7, 10; EX1003, §III.C.)

Incorporating collagen into fibrous scaffolds was also known to enhance their biological properties. (EX1003, §III.C.E; EX1003, ¶54.) Collagen, a polymer and the main component of the extracellular matrix (ECM), is ideal for biomedical applications. It is biocompatible, promotes cell attachment, and significantly boost cell proliferation in fibrous scaffolds. (EX1006, 6-7; EX1009, [0004], [0006], [0136]; EX1018, [0056], [0067]; EX1003, ¶54.) Dr. Simpson, Petitioners' declarant, pioneered incorporating collagen into electrospun fibrous scaffolds for biomedical applications in the early 2000s. (EX1009, Abstract.) Collagen, however, does have a few natural limitations: it degrades quickly and is weak. (EX1005, 1791; EX1003, ¶55.) There were well-known ways to overcome these limitations to create stable collagen-containing fibers, including combining the collagen with other materials. (EX1005, 1791; EX1003, ¶55.) For example, combining collagen with other polymers, such as polycaprolactone or "PCL," was known to improve the strength and stability of the electrospun fibers, and PCL-collagen composite scaffolds were known to have preferable biomechanical properties. (EX1011, [0052]; EX1003, ¶55.) Additionally, crosslinking, a chemical technique that creates additional bonds between atoms, was another well-known way to improve collagen's stability and strength in fibrous scaffolds. (EX1009, [0011], [0136], [0137]; EX1006, 7; EX1005, 1791; EX1003, ¶55.)

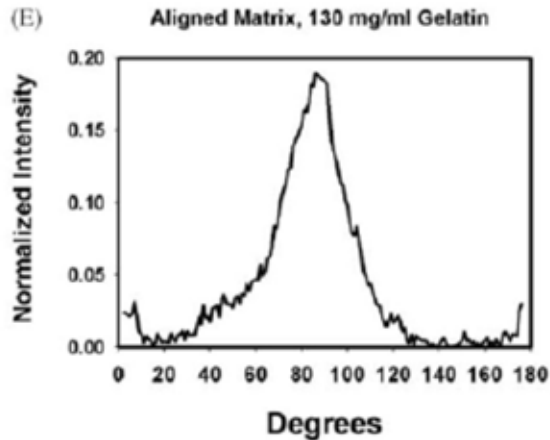
### C. Determining Fiber Alignment Through FFT Analysis

As discussed above, the alignment of fibers within a fibrous scaffold impacts the scaffold's mechanical and biological properties. Thus, to quantify fiber alignment, Dr. Simpson, Petitioners' declarant, adapted a method that can be used to measure fiber alignment, which as set forth below is incorporated into the specification of the '227 patent and is recited in the claims. The details of this method are discussed more fully in Dr. Simpson's declaration. (EX1003, §III.D.)

The method uses a mathematical tool called fast Fourier transform (2D FFT) in order to generate a 2D FFT alignment plot. (EX1013, 4; EX1010, 609; EX1003, ¶¶38-39.) The plot illustrates the degree of fiber alignment, with the shape of its peaks indicating the extent of alignment in the original scaffold. (EX1013, 4; EX1010, 610; EX1003, ¶42.) Randomly aligned fibers produce many short peaks (see figure below), while aligned fibers show a single peak between 0° and 180° with another peak 180° from the first (see figure below). (EX1013, 12; EX1010, 608, 614; EX1003, ¶44.)



(EX1013, 15 (Unaligned 2D FFT alignment plot).)



(EX1013, 15 (Aligned 2D FFT alignment plot).)

Typical practice was (and is) to report 2D FFT alignment plots from 0° to 180°, because the FFT, through its inherent mathematical properties, produces a symmetrical plot. Thus, according to Dr. Simpson’s seminal papers on the method, reporting beyond 180° is unnecessary. (EX1013, 4; EX1010, 609; EX1003, ¶47.) “Typically, the [FFT] data from this analysis is reported for 0° to 180°; the frequency plot is symmetric so a complete summation from 0° to 360° is not technically necessary.” (EX1010, 609; EX1003, ¶63.) Therefore, a single peak in a 2D FFT alignment plot from 0° to 180° indicates that the plot from 0° to 360° has adjacent major peaks that are 180° apart from each other. (EX1003, §III.D, ¶46.)

#### **D. Previously Developed Aligned Collagen Scaffolds**

As discussed above, incorporating aligned collagen fibers into fibrous scaffolds offers substantial benefits for tissue healing and regeneration. Thus, by March 2013, numerous scaffolds with aligned collagen fibers had been developed.

(EX1005, 1793; EX1011, Fig. 9(b), [0019]; EX1016; EX1015, 3778-3781; EX1003, §III.F.) Several of these scaffolds were analyzed using Dr. Simpson's FFT method. That analysis revealed a single major peak in their 2D FFT alignment plots from 0° to 180° degrees, indicating fiber alignment. (EX1005, 1793; EX1016, 634; EX1003, ¶57.) Since the 2D FFT plot from 180° to 360° repeat the same peaks as the plot from 0° to 180°, these scaffolds exhibited adjacent major peaks 180° apart.

## **VI. THE '227 PATENT**

The '227 patent is a divisional application of U.S. Application No. 14/776,106 ("the '106 Application"). The '106 Application resulted in U.S. Patent the '223 Patent. The '223 patent issued with 15 claims. The independent claim, claim 1 is directed to scaffolds that include collagen, wherein an FFT analysis shows major peaks 180 apart. The dependent claims are directed to additional scaffold properties, as well as methods of culturing cells on the scaffold, and methods of differentiating cells on the scaffold.

The '227 patent recites methods of using the scaffold recited in claim 1 of the '223 patent to treat a tissue defect by applying the scaffold to the tissue defect to repair a tendon, ligament, or nerve in need of repair. The '227 patent also has claims that recite culturing cells on a scaffold and promoting cell differentiating

cells on the scaffold. As discussed in more detail below, the claims of the '227 patent are either anticipated and/or obvious for reasons set forth below.

**A. The Subject matter of the '227 Patent**

As a divisional application, the '227 patent shares essentially the same specification as the '223 patent. According to the specification, the invention disclosed therein “relates to a scaffold comprising one or more electrospun fibers.” (EX1001, Abstract; EX1003, §IV.) In some embodiments, the specification states that the fibers of the scaffold are aligned such that “a fast Fourier transform (FFT) analysis result of the fibers [in the scaffold] have adjacent major peaks about 180° apart from each other.” (*Id.*, 13:25-28.) According to the specification, “the major peaks . . . refer to peaks higher than the average peaks, in the result.” (*Id.*, 13:28-29.)

The specification states that “the FFT analysis may be performed by the methods described in *Measuring fiber alignment in electrospun scaffolds; a user's guide to the 2D fast Fourier transform approach*,” Ayres C.E., Jha B.S., Meredith H., Bowman J.R., Bowlin G.L., Henderson S.C., and Simpson D.G, Biomater Sci Polym Ed. 2008; 19(5): 603-21, which is incorporated by reference in its entirety herein.” (*Id.*, 13:40-46.) Dr. Simpson, whose declaration is included herein, is the senior author of the Ayres paper. (EX1003, §§I.A.-C.)

As described in Ayres, in conducting an FFT analysis, peaks can be measured from 0° to 360°. (EX1003, ¶47). The analysis, however, need only be reported from 0° to 180°. (EX1003, ¶47) This is because the peaks from 180° to 360° are repeats of the peaks from 0° to 180°. (*Id.*, ¶47.) As stated by Ayres, which the '227 patent incorporates in its entirety, “[t]ypically, the [FFT] data from this analysis is reported for 0° to 180°; the frequency plot is symmetric so a complete summation from 0° to 360° is not technically necessary.” (EX1010, 609; *see also* 13:38-46.)

FIG. 8 of the '227 patent, reproduced below, discloses the results of an FFT analysis of fibers prepared by the Applicants: “FIG. 8 . . . depicts exemplary FFT analysis results [(a)] of the fibers described herein . . . and [(b)] a control sample.” (*Id.*, 2:10-12.) The specification further states that “[i]n some embodiments, FFT result of the fibers described herein may have adjacent major peaks with about 180° apart from each other as shown in FIG.8A.” (*Id.*, 13:46-49.)

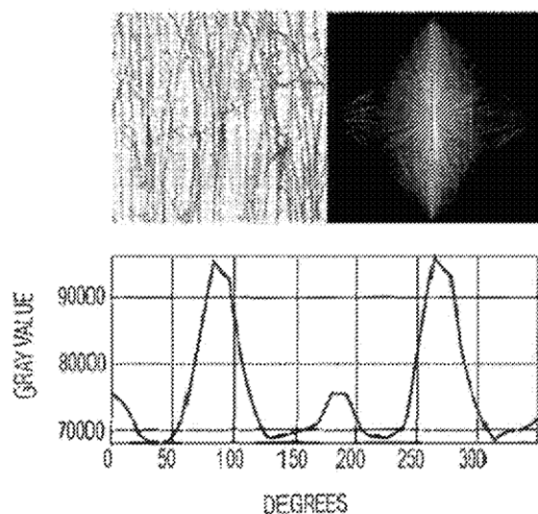


**FIG. 8A**

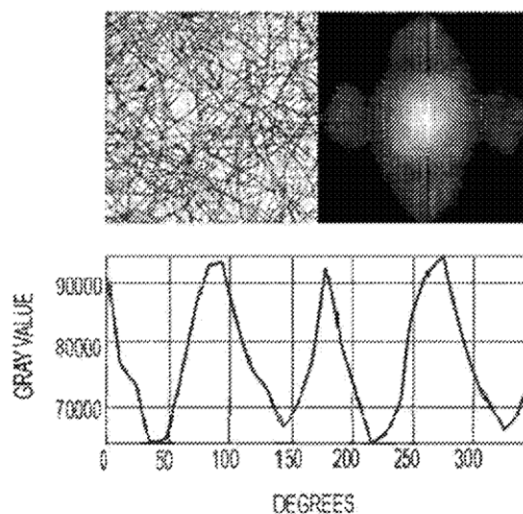


**FIG. 8B**

In FIG. 8A, the FFT analysis shows aligned fibers that have major peaks at about 90° and 270°. Thus, these major peaks are about 180° apart from one another (270° minus 90°=180°), and there are no other major peaks. (EX1003 ¶65.) As noted above, and according to Ayres, which the specification incorporates for the performance of the FFT method, the graph in FIGS. 8A would only need to be reported through 180°. (EX1010, 609; EX1001, 13:38-49; EX1003, ¶ 65.) This is because the peaks from 0° to 180° are symmetrical to the peaks from 180° to 360°. (*Id.*) Thus, even if FIG. 8A only reported data from 0° to 180°, a POSA would understand that the sample in FIG. 8A would necessarily have a second peak at about 270° and no other because of the symmetry discussed in Ayres above and because there are no other major peaks appearing in the 0-180° range. (EX1003, ¶65.) In contrast, the control sample in FIG. 8B, shows peaks at

about 0°, 90°, 180°, and 270°. (EX1003, ¶67.) These fibers do not appear aligned, as shown in FIG. 8B. (EX1003, ¶67.) Like above, and according to Ayres, the graph in 8B would only need to be reported to 180°.

The '227 patent states that “[i]n some embodiments, the aligned fiber and/or electrospun fiber in the scaffold is crosslinked.” (*Id.*, 15:16-17.) The '227 patent explains that the crosslinking may be obtained “by any conventional chemical crosslinking method.” (EX1001, 12:52-54.)

The '227 specification states that the invention “relates to methods of promoting nerve repair using the aligned fiber, electrospun fiber, and/or scaffold described herein.” (*Id.*, 16:53-55.) In terms of implanting the scaffold, the specification states that “the tissue defect may be treated by applying an elongated sheet described herein to surround the defect, or by applying an elongated roll implant described herein between the tissue defect or gap.” (EX1001, 19:9-12.) “Optionally, the elongated sheet may be applied around the tissue defect, and/or the elongated roll implant may be applied to facilitate surgery and healing.” (EX1001, 19:15-17.)

The '227 patent specification also describes methods for culturing cells “on the scaffold or aligned fiber.” (*Id.*, 16:26-27.) The “method may further comprise culturing dorsal root ganglia and/or stem cells on the aligned fiber, electrospun fiber, and/or scaffold prior to implanting.” (*Id.*, 16:60-62.) The specification states

that “growing and/or culturing cells on a scaffold” includes “traditional cell culture methods as well as placing on a surface any setting, such as in natural or synthetic biocompatible matrices or tissues.” (*Id.*, 16:31-36.)

## **B. The Claims**

The '227 patent contains 14 claims, three independent claims (reproduced below) and 11 dependent claims. These claims were pursued as a divisional application from the '106 application, which resulted in the '223 patent. While claim 1 of the '227 patent (and claims 2-6 that depend from it) require collagen as a component of the fibers of the scaffold, claim 7 (and its dependent claims) do not.

Independent Claim 1 recites: “A method of treating a tissue defect in a subject comprising implanting at the tissue defect a scaffold comprising crosslinked fibers comprising collagen wherein a result of a fast Fourier transform (FFT) analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other, and applying the scaffold to the tissue defect to repair a tendon, a ligament or a nerve defect.” (EX1001, Claim 1.)

Independent claim 7 recites: “A method of cell culture comprising [1] placing cells on a scaffold comprising aligned fibers, wherein a result of a FFT analysis of the fibers demonstrates that the fibers have major adjacent peaks that

are about 180° apart from each other, and [2] growing the cells in conditions suitable for the cell culture.”

### **C. The Prosecution History**

The '223 patent, which is the parent of the '227 patent, issued on November 27, 2018. It issued from U.S. Application No. 14/776,106 filed September 14, 2015. The face of the patent also lists a provisional application, Provisional App. No. 61/785,031, which was filed on March 14, 2013.<sup>2</sup> Both the '223 and '227 patents claim priority to this provisional application. As shown below, as early as 2011, the prior art disclosed scaffolds with electrospun fibers comprising collagen with aligned peaks about 180° apart as measured using an FFT analysis. This is *before* the date of the provisional application—the earliest date the claims of either the '223 or '227 patents could possibly claim priority to. Thus, Petitioners need not challenge the March 14, 2013, priority date unless necessary to do so in response to the arguments made by the Patent Owner.

#### **1. The '106 application leading to the '223 Patent**

The '106 application received one office action rejection before allowance. The Examiner rejected then pending claims 1, 11, 12, and 17 (corresponding to

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<sup>2</sup> In the *LifeNet v. Embody* Litigation, LifeNet has asserted that its invention date was March 14, 2013.

allowed claims 1, 4-6, respectively), as anticipated under 35 U.S.C. 102(b) by Huang, et al., *Electrospun collagen-chitosan-TPU nanofibrous scaffolds for tissue engineered tubular grafts*, 82 Colloids and Surfaces B: Biointerfaces 307-315 (2011) (referred to herein as “Huang1”). The Examiner stated that “Huang discloses a scaffold comprising one or more electrospun fibers” where the “aligned nanofibrous scaffolds” were “based on collagen, chitosan, thermoplastic polyurethane (TPU) blends” and showed peaks about 180° apart from each other in a FFT analysis. (EX1007, 210.)

The Applicant responded to the anticipation rejection, arguing that the prior art fibers disclosed in Huang1 satisfied the claimed alignment but for “*only* pure thermoplastic polyurethane fibers that comprise *no collagen*.” (EX1007, 238 (emphasis added).) According to the Applicant, Huang1 discloses the use of collagen in the fibers, but these fibers were *not* aligned. (*Id.*) The Applicant thus amended independent claim 1 to *require* the inclusion of collagen. Because the pending dependent claims depended from claim 1, the amendment to include collagen applied to those claims as well.

The Examiner further rejected pending claims 1, 5-6, 11-12, 17, 19, and 20-22 (corresponding to allowed claims 1, and 2-10, respectively) as obvious under 35 U.S.C. 103(a) by U.S. Patent App. Pub. No. 2004/0037813 (“Simpson”). (EX1007, 210-13.) The Examiner explained that based on Simpson, a POSA

“would have had a reasonable expectation of success in producing the claimed invention.” (EX1007, 210-13.)

The Applicant overcame Simpson by arguing that the scaffold in Simpson was prepared the same way as the scaffold described in Huang1, and because Huang1 was not able to obtain aligned fibers with collagen (according to the Applicant), a skilled artisan following Simpson would also not be able to achieve aligned collagen fibers either. (EX1007, 238-39.) Thus, a POSA “would not have expected to obtain the claimed fiber alignment” following the Simpson reference. (*Id.*)

On June 12, 2018, the Examiner issued a notice of allowance for claims 1, 5, 6, 11, 12, 17, 19, 20, 21, and 22, that were examined during prosecution, but *also* included claims 27-28, and 31-33, that had been previously *withdrawn* in response to a restriction requirement. The Examiner found the withdrawn claims, amended to depend from claim 1, which required the presence of collagen in the fibers, were “directed to the process of making or using an allowable product, previously withdrawn from consideration as a result of the restriction requirement” and were thus rejoined. (EX1007, 249.)

## **2. The '159 application leading to the '227 Patent**

The application underlying the '227 was filed a month later, on July 25, 2018 as Patent Application No. 16/045,159 and, as mentioned above, is a

divisional application of U.S. Patent Application No. 14/776,106, which issued as the '223 patent. The Examiner for the '159 application, however, was not the same as the Examiner who examined the '061 application.

In the '159 divisional application, the Applicant pursued claims 25-35 that were originally included in the '106 Application. Claims 25, 26, 27, and 31 were independent, and claims 25, 27, and 31 were ultimately renumbered to claims 1, 7, and 11, respectively. It should be noted that independent claims 27 and 31 (issued as claims 7 and 11), as prosecuted in the '159 application, did *not*, and were in fact *never* amended, to require the presence of collagen, which—as discussed above—was an essential amendment during the prosecution of the '106 patent application to avoid Huang1. The different examiner involved in the '159 application, however, did not raise a prior art rejection based on Huang1. Rather, the prosecution history of the claims that ultimately issued in the '227 patent focused primarily on 35 U.S.C. § 112, with the Examiner rejecting the presented claims as both indefinite and non-enabled.

In response to such rejections, the Applicant amended the pending claims and added new claims 36-45. (EX1002, 524-26.) Applicants stated they amended the claims “to provide additional elements and further clarity” to both overcome the indefiniteness and enablement rejections. (EX1002, 527.) The Applicants amended claim 25, which ultimately issued as claim 1, to indicate where the tissue

defect and the applying step occurs by adding the following language to the claim:

“implanting at the tissue defect” the scaffold that has the claimed properties.

(EX1002, 524.) Further, the applicants also addressed the Examiner’s concern about the breadth of the claims by adding language that limited the type of tissue defect to be treating, adding language that the purpose of implanting the scaffold is “to repair a tendon, ligament, or never defect.” (*Id.*) The Applicant also amended claim 1 and the claims that depended from it to include collagen and to be crosslinked. These amendments were made without the Examiner’s prompting.

After additional prosecution, the Applicant and the Examiner had an interview where it was agreed that the Applicant will submit a terminal disclaimer to any patent term that would extend beyond the term of the parent ’223 patent because claims 11-15 of the ’223 patent “were found to overlap the instant claims 27-33 and 35.” (EX1002, 663.) The Examiner stated that with this terminal disclaimer in place, the case would be in condition for allowance. (*Id.*) The Applicant submitted the terminal disclaimer, and the Examiner issued the Notice of Allowability on February 28, 2022. (*Id.* at 668.)

## **VII. LEVEL OF ORDINARY SKILL IN THE ART**

A POSA relevant to the ’227 patent would be a Ph.D. student with a minimum of two years of experience in their faculty advisor’s laboratory. At the relevant time, a POSA would have understood the following technologies and

techniques: electrospinning fibers, including for tissue engineering, tissue engineering techniques, and using FFT analysis and performing such analysis.

(EX1003, §II.C.)

Dr. Simpson is an expert in electrospinning collagen and other components for the preparation of scaffolds and has experience in culturing various types of cells on to scaffolds. (EX1003, §I.B.) Dr. Simpson also has extensive experience in FFT analysis of electrospun fibers and is one of the authors of the primary references in the field. (EX1003, §I.B.) His article is referenced in the '227 patent to describe the methods of performing the FFT analysis required by the claims of the '227 patent. (EX1003, ¶62.) His Declaration and CV are attached as Exhibits 1003 and 1004, respectively.

### **VIII. CLAIM CONSTRUCTION**

For purposes of this Petition, Petitioners do not believe that any claims require construction in view of the prior art being presented. To the extent the Patent Owner identifies terms for construction, Petitioners reserve the right to respond.

## IX. SUMMARY OF THE ASSERTED PRIOR ART

### A. Kuo et al., U.S. Patent Application No. US 2011/0293685 A1, Pub. Date Dec. 1, 2011

Kuo is U.S. Patent Application No. US 2011/0293685 A1, which published on December 1, 2011. Kuo is therefore prior art to the '227 patent under 35 U.S.C. §§ 102(b) and 103(a). Kuo was not cited during prosecution of the '227 patent.

Kuo, entitled “Scaffolds For Tissue Engineering And Regenerative Medicine,” discloses electrospun collagen/PCL scaffolds for “tissue repair” that are seeded with cells and formed into a desired shape to replace tissue including muscles, *ligaments, tendons, and nerves*, among others. (EX1018, Title, Abstract, [0005], [0052], [0113] (emphasis added).) The scaffolds described in Kuo are created by electrospun micro or nano fibers with “fiber orientation that is random, *aligned*, or any combination thereof.” (EX1018, [0005] (emphasis added).) Figure 3 “is a diagram depicting an exemplary method for making random or aligned fibers in a scaffold mat.” (EX1018, [0030].) Figure 4 “is a set of micrographs depicting FD-SEM images of *aligned* nanofiber scaffolds.” (EX1018, [0031] (emphasis added).) Kuo reports how their “[a]ligned nanofiber scaffolds were seeded with progenitor cells and subsequently rolled with the leading edge parallel to the axis of alignment.” (EX1018, [0112].) Kuo explains that “[t]his aligned nanofiber scaffold locally mimicked the native microstructure of tendon/ligament (aligned collagen fibrils), globally mimicked a fascicle or bundle in

tendon/ligament tissue, and resulted in cell seeding throughout the construct.” (*Id.*) Kuo further notes that the fibers may be comprised of natural materials or synthetic materials or a combination of both and can include collagen. (EX1018, [0005], [0014].)

Kuo describes the cells that can seed the scaffold as “selected from the group consisting of stem cells, osteoblasts, myoblasts, neuroblasts, fibroblasts, glioblasts, germ cells hepatocytes, chondrocytes, keratinocytes, smooth muscle cells, cardiac muscle cells, connective tissue cells, epithelial cells, endothelial cells, hormone-secreting cells, neurons, tenocytes, skeletal myocytes, and skeletal myoblasts.” (EX1018, [0016]; [0058]-[0066]; EX1003 §V.A.)

**B. Lee et al., U.S. Patent Application No. US 2010/0331980 A1, Pub. Date December 1, 2011**

Lee is a U.S. Patent Application No. US 2010/0331980 A1, which published on December 30, 2010, which is more than a year before the date of the first priority application of the '227 patent, which is March 14, 2013, and is prior art under at least Pre-AIA 35 U.S.C. §§ 102(b) and 103(a) as of December 30, 2010. (EX1011.) Lee was not cited as prior art during the prosecution of the '227 patent.

Lee teaches that the reconstruction of skeletal muscle tissue due to a traumatic injury is difficult because of the lack of “functional muscle tissue substitutes.” (EX1011, [0003].) To solve this problem, Lee describes engineered muscle tissue, including “a biodegradable scaffold comprising a plurality of fibers

oriented along a longitudinal axis of the fibers” and “crosslinking said fibers to form the scaffold.” (EX1011, [0005]-[0006]; EX1003 §V.B.)

Lee further describes using fibers for the scaffold that are natural, such as collagen, or synthetic, such as PCL, or blends of natural and synthetic fibers between 2:1 and 1:2 by weight. (EX1011, [0005].) Lee electrospun nanofiber meshes “using a blend of PCL and collagen with a ratio of 1:1 in weight.” (EX1011, [0062]-[0063].) Lee further explained that “[a]fter the fabrication process, the electrospun PCL/collagen nanofiber meshes were cross linked under vapor of 2.5% glutaraldehyde solution for 6 hr to increase stability and strength of collagen. The degrees of cross-linking were measured by Ninhydrin assay.” (EX1011, [0063].)

Further, to approximate skeletal muscle, Lee fabricated “nanofiber meshes that are aligned in a unidirectional manner to facilitate myotube formation.” (EX1011, [0090].) Lee explains that previous studies demonstrated that “aligned nanofibrous structures can be obtained using a variety of collecting mandrel systems, including rotating drum.” (EX1011, [0091].) Lee discovered that “[f]iber alignment had a profound effect on the mechanical properties of electrospun PCL/collagen nanofiber meshes,” including increased “tensile strength of the aligned nanofiber meshes.” (EX1011, [0081].)

Further, Lee explains that the aligned fibers aided in cell growth: “[a]ligned nanofibers greatly influenced muscle cell organization and enhanced myotube formation. The myotubes formed on the aligned nanofiber meshes were highly organized and were significantly longer than that of the myotubes on the randomly oriented meshes. These findings indicate that the electrospun PCL/collagen nanofiber meshes are able to guide and orient skeletal muscle cells into organized structures that mimic native tissues.” (EX1011, [0094], *see also* [0084]-[0085].)

**C. Huang et al., The Involvement of Integrin  $\beta$ 1 Signaling in the Migration and Myofibroblastic Differentiation of Skin Fibroblasts on Anisotropic Collagen-Containing Nanofibers, Biomaterials 33 (2012) 1791-1800, available online 2 December 2011 (“Huang2”)**

Huang2 published online on December 2, 2011, which is more than a year before the date of the first priority application of the ’227 patent, which is March 14, 2013, and is prior art under at least Pre-AIA 35 U.S.C. §§ 102(b) and 103(a) as of December 2, 2011. (EX1005.)<sup>3</sup> Huang2 is a different prior art reference from a different research group than the Huang reference (referred to Huang1) that is

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<sup>3</sup> Huang2 on its face shows that it was publicly available online on December 2, 2011, which is confirmed by a declaration from Emma Xu, a custodian for the publisher, submitted with this petition. (EX1020) Further, a hard copy of Huang2 obtained from the National Library of Medicine, has a date stamp, indicating it received a copy of Huang2 on February 21, 2012.

discussed above. Huang2 was not cited as prior art during the prosecution of the '223 or '227 patents.

Huang2 concerns the use of skin grafts in treating tissue injuries. (EX1005, 1791; EX1003, §V.C.) In determining the most beneficial properties for growing cells on a scaffold, Huang2 studied fibers comprising collagen and sought to examine the effect of *aligned* fibers compared to *non-aligned* fibers on the attachment and growth of normal human dermal fibroblasts (“NHDFs”), including fibroblast-to-myofibroblast differentiation. (EX1005, 1797.) Huang2 sought to “understand how various nanofibrous matrices regulate skin cell behaviors and intracellular signaling pathways.” (EX1005, Abstract.) In Huang2’s study, “the phenotypic expressions of normal human dermal fibroblasts (NHDFs) on collagen-containing matrices with either isotropic (i.e., fibers collected randomly with *no alignment*) or anisotropic (i.e., fiber collected with *alignment*) were studied . . . .” (EX1005, Abstract (emphasis added).) Huang2’s results showed, among other things, that the fibroblast-to-myofibroblast differentiation was greatly enhanced for the NHDFs cultured on the anisotropic or aligned nanofibrous matrices comprising collagen, likely due to the impact of the alignment on the integrin  $\beta 1$  signaling pathway. (EX1005, 1797, 1799, Abstract.)

Huang2 discloses the importance of collagen in electrospinning fibers in tissue engineering due to its “contribution to skin integrity.” (EX1005, 1791.)

Huang2 also recognized that in utilizing collagen fibers, “either crosslinking or combination with other materials is necessary to obtain a stable scaffold.”

(EX1005, 1791.) In Huang2, “nanofibrous matrices of PCL and Collagen at a weight ratio of 3:1 were fabricated using electrospinning previously as previously described.” (EX1005, 1792.)

To determine and show the alignment of the fibers used in the scaffolds, Huang2 performed FFT analyses, The result of these FFT tests are reported in Huang2 and depicted in Figure 1:

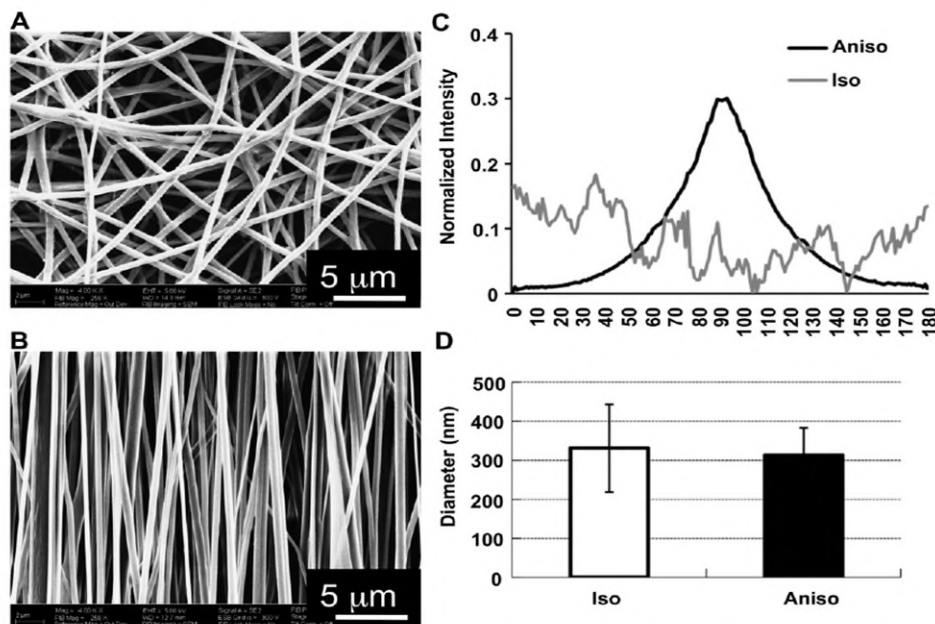


**Fig. 1.** Characterization of isotropic and anisotropic electrospun PCL/Coll nanofibrous matrices. SEM image of nanofibrous matrices with two types of fiber spatial organizations: isotropic (A) and anisotropic (B). (C) Normalized intensity plots against the angle of acquisition for isotropic and anisotropic nanofibrous matrices. (D) The measured average fiber diameter based on SEM images. Scale bar: 5 μm.

These images show the anisotropic (aligned) fiber sample (EX1005, Figure 1B) and the isotropic (non-aligned) sample (Figure 1A). (EX1005, 1793.) The FFT analysis graph is also reported (Figure 1C). (EX1005, 1793.) As mentioned

above, Huang2 reports that the anisotropic PCL/collagen nanofibers performed better in promoting certain properties useful in cell growth and wound healing. (EX1005, 1797.)

The aligned sample, referred to as “Aniso,” has one major peak at about 90° with no other major peaks present. (EX1005, 1793.) Based on this readout, and as discussed in detail above, because of the symmetry in an FFT readout between 0° to 180° and 180° to 360°, a POSA would know that if the scale were extended to 360°, a second peak for the Aniso (aligned) sample would necessarily be at the symmetrical position of about 270°. (EX1003, ¶90.) No other major peaks would be present between 180° and 360° for the Aniso (aligned) sample. (EX1003, ¶90.) Therefore, Figure 1C in Huang2 for the Aniso (aligned) sample shows aligned fibers containing collagen that have major peaks 180° apart from each other. (EX1003, ¶90.) For the Iso sample, the FFT readout does *not* show a single major peak between 0° and 180°. (EX1003, ¶90.) Accordingly, the Iso (non-aligned) sample does not have major peaks 180° apart, which would be expected for an unaligned sample.

**X. GROUND 1: HUANG2 IN VIEW OF KUO RENDERS CLAIMS 1-6 OBVIOUS UNDER 35 U.S.C. § 103**

Claims 1-6 of the '227 patent would have been obvious in view of Huang2 when read in combination with Kuo. (EX1003, §VI.A) The point of alleged novelty of claim 1 of the '227 patent is a scaffold with aligned fibers containing

collagen that have peaks 180° apart, as measured by FFT. As discussed above and in detail below, Huang2 describes such a scaffold. Further, the other elements of claim 1, such as using that scaffold to treat a tissue injury, is the primary purpose of tissue engineering and is disclosed in multiple references, including Huang2 and Kuo. Similarly, many references teach crosslinking collagen fibers to improve its stability and structural integrity, including both Huang2 and Kuo.

Moreover, a POSA would have had the necessary motivation to combine Huang2 and Kuo because both are in the same field of art, and both seek to solve the same problems. (EX1003, ¶96.) Huang2 seeks to create a stable scaffold “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).” (EX1005, 1791.)

Similarly, Kuo, which is in the same field, discloses electrospun collagen/PCL scaffolds that are seeded with cells and formed into a desired shape to replace tissue including muscles, ligaments, tendons, and nerves, among others, to repair various tissue injuries. (EX1018, Title, Abstract, [0005], [0052], [0113].) Kuo discusses the benefits of “mimic[ing] the native microstructure” of damaged tissue with engineered electrospun fiber scaffolds to support cell growth and stem cell differentiation, such that various injuries can be repaired and tissues regenerated, including injuries to muscle, tendon, ligament or other connective

tissue.” (EX1018, [0003]-[0004], [0006], 0112].) “In one embodiment, the compositions are used for muscle, tendon, ligament or nerve repair, replacement or regeneration strategies.” (EX1018, [0067].) Kuo further teaches that a wide range of cell types can be used “depending upon the intended function of the tissue engineered construct being produced.” (EX1018, [0058].)

Accordingly, a POSA would have been motivated and able to use a scaffold comprising Huang2’s aligned fibers—as shown by FFT analysis—containing collagen, which may be cross-linked, to treat a tendon, ligament, or nerve defect as taught by Kuo. Huang2 specifically explains how aligned fibers are beneficial for cell growth, which provides further motivation to combine the two references, particularly where the target tissue is a tendon or ligament where it is important that cells grow in an aligned manner. (EX1003, ¶98.) Indeed, Kuo teaches that aligned fibers are desirable to mimic the native structure of a tendon/ligament. (EX1018, [0112].) And a POSA would have been able to do so using well-known established methods described in both Huang2 and Kuo to achieve predictable results with a reasonable expectation of success. (EX1003, ¶102.) This is particularly so as both Huang2 and Kuo successfully created scaffolds containing fibers containing blends of collagen and PCL, and both Huang2 and Kuo reported obtaining aligned fibers. (EX1003, ¶¶94-102.)

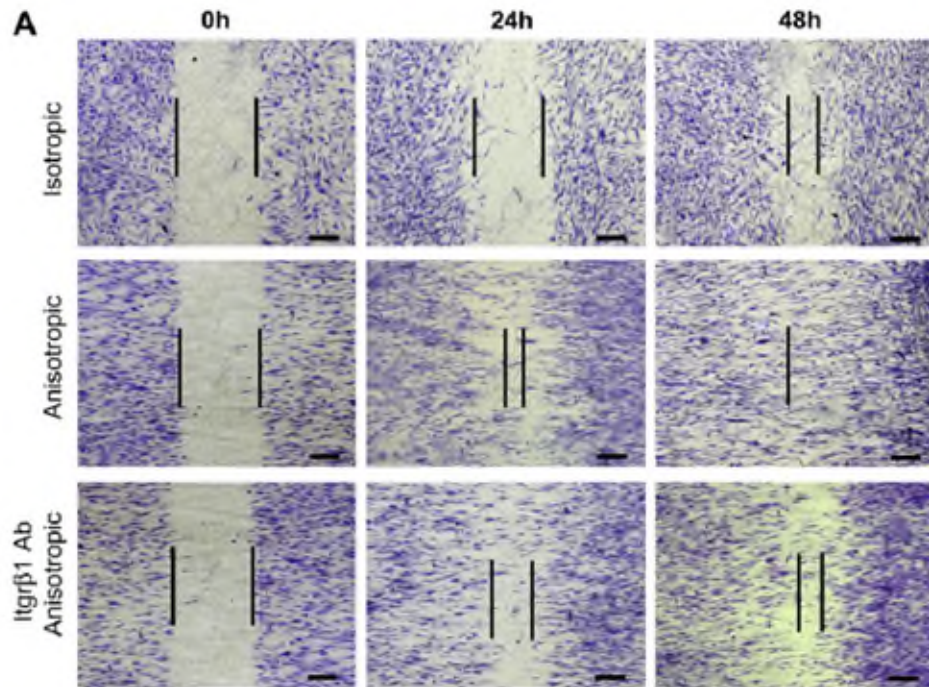
**A. Claim 1**

Claim 1 of the '227 patent recites “A method of treating a tissue defect in a subject comprising implanting at the tissue defect a scaffold comprising crosslinked fibers comprising collagen wherein a result of a fast Fourier transform (FFT) analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other, and applying the scaffold to the tissue defect to repair a tendon, a ligament or a nerve defect.” This claim would have been obvious in view of Huang2 when read in combination with Kuo. (EX1003, §VI.A.1.)

**1. “A method of treating a tissue defect in a subject comprising implanting at the tissue defect a scaffold”**

Huang2 by itself discloses this element of the claim. (EX1003, §VI.A.1.a.) Huang2 scaffolds are designed to treat a tissue defect in a subject, i.e., a wound in the skin. (EX1005, 1791.) Huang2 contemplates implanting the scaffold in a subject and explains that “during normal wound healing the fibroblast-to-myofibroblast differentiation can facilitate wound closure by drawing the wound margins together, however, it would also result in scar formation if the proper apoptosis of myofibroblasts does not occur upon the cease of wound contraction. Therefore, the fibroblast-to-myofibroblast differentiation needs to be appropriately balanced for minimum scar formation during the wound healing.” (EX1005, 1792.)

Huang2 further discloses a “wound healing assay” wherein nanofibrous matrices are seeded with fibroblasts for wound treatment, (*Id.*, 1793, 1796), as shown in Figure 6A:



(EX1005, 1797, Figure 6A.) Indeed, one of the goals of Huang2 is to understand “how various nanofibrous matrices regulate skin cell behaviors and intracellular signaling pathways.” (EX1005, Abstract.) This is important, according to Huang2, to fine tune “the functionality of tissue-engineered skin grafts and *affecting the wound healing process.*” (*Id.*) Accordingly, this element of the claim is disclosed by Huang2 by itself.

Further, as set forth in § X.A.4., *infra*, Kuo also specifically discloses implanting an electrospun scaffold at a tissue defect to treat an injury. (EX1018,

Title, Abstract, [0005-0006], [0022-0023], [0034], [0052], [0067], [0112]-[0113].)

For the reasons set forth above, a skilled artisan would have been motivated with a reasonable expectation of success to utilize Huang2 aligned fibers to treat one of the tissue defects described in Kuo.

**2. “a scaffold comprising crosslinked fibers comprising collagen”**

Huang2 by itself describes this claim element. (EX1003, §VI.A.1.b.)

Huang2 shows the creation of electrospun nanofibers containing collagen.

(EX1005, 1792.) Huang2 describes electrospinning “[n]anofibrous matrices of PCL and *Collagen*” from an “8% (w/v) solution of 3:1 PCL/Coll” with an electrospinning device. (EX1005, 1792.) Huang2 further explains that “[e]lectrospinning a blend solution of collagen and polycaprolactone (PCL) . . . can yield rather stable nanofibers.” (EX1005, 1791.) Further, Huang2 states that alternatively “crosslinking” can be used to “obtain a stable scaffold.” (EX1005, 1791.)

Kuo also discloses scaffolds comprising crosslinked fibers comprising collagen. To fabricate the scaffold, Kuo electrospun a blend of “PCL:collagen type I” and then seeded the scaffold with mesenchymal progenitor cells. (EX1018, [0013]-[0014].) Kuo also discloses the crosslinking element of the claim. Kuo specifically incorporates by reference a paper by Meinel, et al., 2004, *Biotechnol.*

Bioeng. 88:379-391 (EX1023), for the teaching of how to prepare scaffold from electrospun fibers. (EX1018, [0040].)

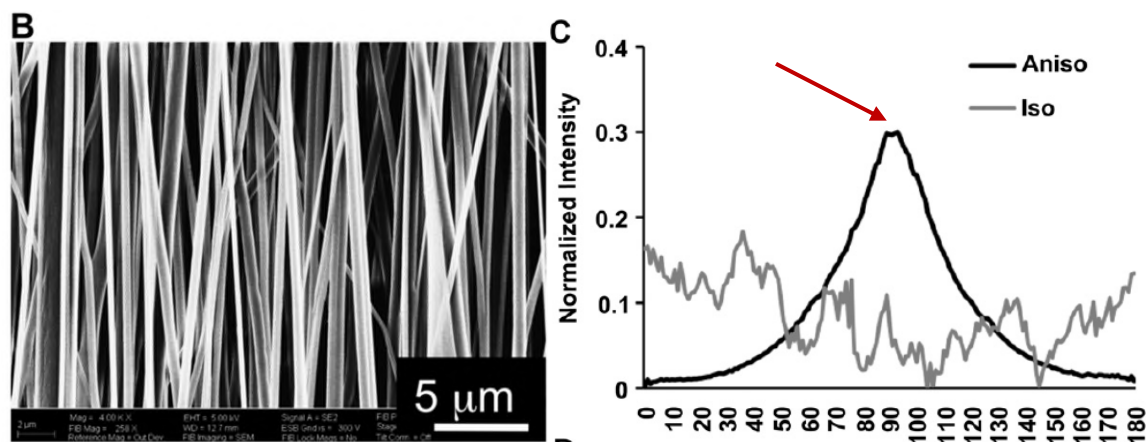
Meinel, as incorporated into Kuo, discloses that although “[c]ollagen is frequently used as a scaffold material because it is a major component of the cartilage matrix . . . its rapid degradation has been recognized as a limitation.” (EX1023, 380.) Meinel explains that crosslinking collagen scaffolds can address this issue by “decreas[ing] the rate of degradation of collagen by two orders of magnitude.” (EX1003, ¶112; EX1023, 380-81, 390.) And Meinel teaches that collagen scaffolds can be crosslinked with EDC/NHS. (EX1023, 380-81.) Meinel specifically states at pages 380-81 that “[t]o reduce the rate of degradation, in some experiments the collagen scaffolds were cross-linked using the ethyl-3-(3-dimethyl aminopropyl) carbodiimide hydrochloride/N-hydroxy succinimide (EDC/NHS) chemistry previously established for collagen films and fibers. . . .” (EX1023, 380-81.)

Accordingly, for the reasons set forth above, a skilled artisan would have been motivated with a reasonable expectation of success to utilize Huang2’s aligned fibers to create a scaffold that can treat a tissue defect, and would have been motivated to improve the stability of collagen fibers by chemically crosslinking, as taught by both Huang2 and Kuo.



was performed on [Huang2]’s SEM images . . . to characterize the anisotropy [alignment] and assign a numerical value to fiber orientation.” (*Id.*; *see also id.* 1792 (describing FFT analysis using ImageJ).)

To perform its FFT analysis, Huang2 uses the same ImageJ software to perform the analysis as used in the ’227 patent. (EX1005, 1792, 1794, 1800 (citing EX1013 (Ayres 2006) for the FFT analysis procedure); EX1001, 13:16-23, 21:27-31 (citing EX1010 (Ayres 2008) for the same).) Huang2 graphed its FFT analysis of the aligned (anisotropic) fibers photographed in Figure 1B in Figure 1C, plotting the peaks from 0°-180°:



(Figures 1B, 1C (annotated).)

In Huang2’s Figure 1C above, the FFT result of the anisotropic (aligned) fibers of Figure 1B are shown with the dark line, with a “major peak” around about 90° (annotated with a **red** arrow). (*Id.*; EX1003 ¶120.) Huang2 explains that “[t]he narrow peak of the normalized intensity values in anisotropic [aligned]

matrices (Figure 1C) indicated that *PCL/Coll nanofibers aligned along a single axis* (Fig. 1B).” (*Id.* (emphasis added).)

As typical in the field, and as taught by Ayres, Figure 1C reports its results out to 180°. (EX1003, ¶47, ¶121; EX1010, 609.) As such, and as explained above, because of the intrinsic symmetry of an FFT, Huang2’s FFT analysis would necessarily show a second major peak at around 270° (which is 180° from the 90° peak) if the scale were extended to 0°-360°. (EX1003 ¶121; EX1010, 609.) Thus, a POSA would know from the alignment of the fibers depicted in the image of Figure 1B and the major peak at around 90° in Figure 1C that the fibers are aligned, such that there would necessarily be a second peak about 180° apart at 270°. (EX1003 ¶121; EX1010, 609.)

Finally, Dr. Simpson conducted his own analysis of Figure 1B using the FFT analysis described in Huang2 and the ’227 patent and reported data from 0° to 360°. (EX1003, ¶¶125-126.)

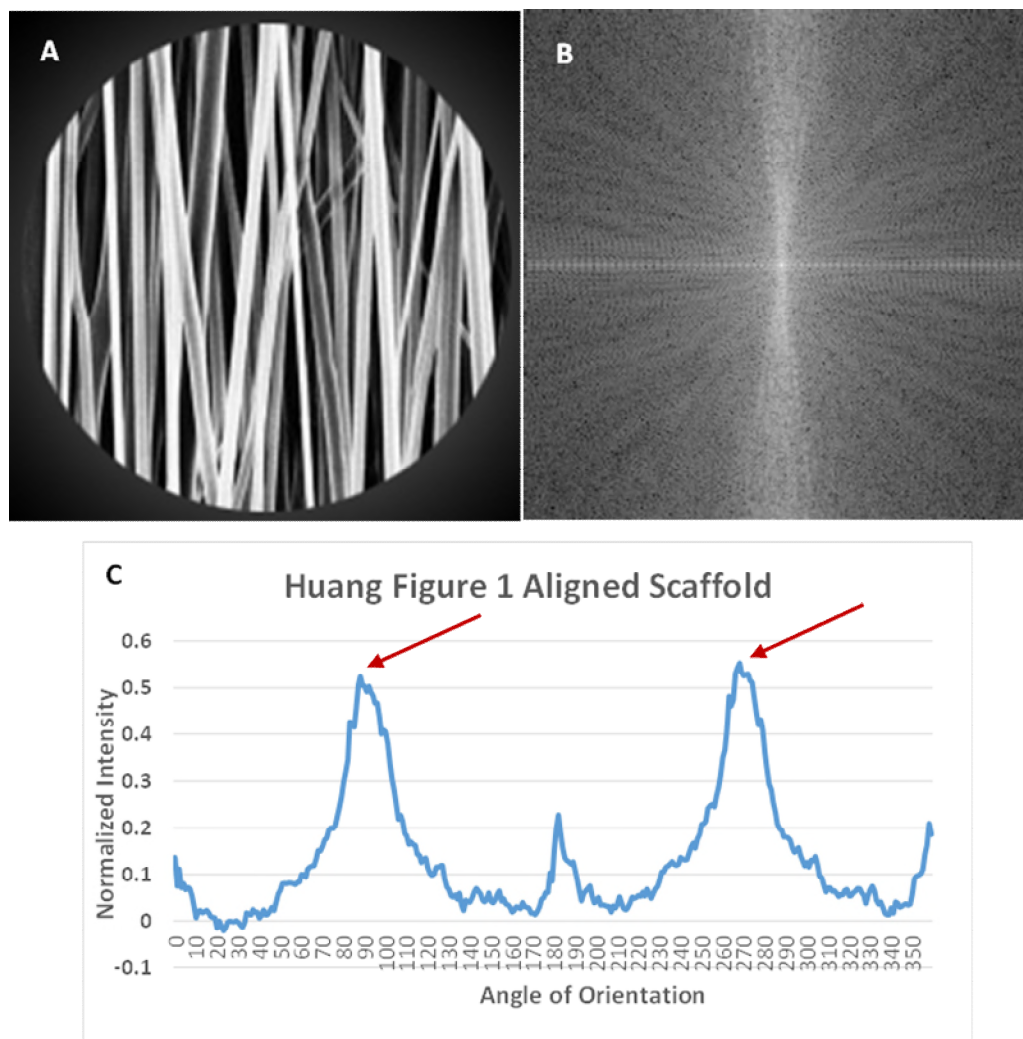


Figure 2. (A) Figure 1 from Huang aligned scaffold cropped and masked for 2DFFT. (B) 2DFFT spectrum of aligned scaffold, the image has been rotated to correct for the rotation intrinsic to the FFT analysis. (c) Normalized intensity values for aligned scaffold 0-360 degrees.

The graph generated from the FFT analysis performed by Dr. Simpson demonstrates that the aligned fibers have a major peak at about 90° and, because Dr. Simpson reported all the peaks through 360°, a second major peak at about 270°, which shows that the peaks are 180° apart as recited in claim 1. (EX1003,

¶126.) The major peaks at about 90° and 270° are annotated with **red** arrows).

(EX1003, ¶126.)

Accordingly, this element of claim 1 is disclosed by Huang2 by itself.

**4. “and applying the scaffold to the tissue defect to repair a tendon, a ligament or a nerve defect”**

This claim element would have been obvious in view of Huang2 combined with Kuo. (EX1003, §VI.A.1.d.) Huang2 discusses using his scaffolds of aligned fibers comprising collagen to repair a tissue injury. Kuo similarly teaches the desirability of using aligned electrospun collagen/PCL scaffolds for “tissue repair” to replace tissue including muscles, ligaments, tendons, and nerves, among others. (EX1018, Title, Abstract, [0005], [0052], [0113].) Kuo specifically discloses a method for “replacing or enhancing a tissue” that comprises “(a) forming a tissue construct by contacting a scaffold sheet of fibrous material with a cell; and rolling the scaffold sheet in a jelly-roll like manner to form a spirally wound tissue construct, (b) implanting the spirally wound tissue construct into a subject in need of tissue replacement or regeneration, wherein the spirally wound tissue construct replaces a tissue.” (EX1018, [0022].) Kuo then states that the tissue to be replaced or regenerated is “selected from the group consisting of a muscle, a nerve, a ligament, a tendon, or another tissue.” (EX1018, [0023].)

As set forth above, a POSA would have been motivated to use Huang2’s aligned fibers, as shown by FFT analysis, which mimic the structure of the natural

tendon, ligament, or nerve, and are stated to improve cell growth, to fabricate a scaffold to treat a tendon, ligament, or a nerve defect as taught by Kuo. (EX1003, ¶131.)

This is particularly so where the structure and function of tendon, ligament, and nerve tissue require that the cells grow in an aligned manner, and the native tissue are aligned. (EX1003, ¶¶133-35.) Indeed, Kuo teaches the desirability of using aligned fibers to mimic native tissues such as tendons, ligaments, and nerves. (EX1018, [0006], [0112]; EX1003, ¶¶133-35.) A POSA would have been well aware of the concept of using scaffolds that mimic the structure and function of native tissues. (EX1018, [0006], [0034,], [0112], EX1019, 27; EX1003, ¶¶133-35.) A POSA also would have known that tendons and ligaments are composed of aligned type 1 collagen and require strength along the axis of alignment, like Huang2's scaffold demonstrated. (EX1019, 3, 32; EX1005, 1794; EX1003, ¶¶133-35.) Further, a POSA would have known that nerves are composed of aligned fibers that induce cell growth along the axis of alignment, like Huang2's scaffold demonstrated. (EX1019, 3, 28; EX1005, 1794; EX1003, ¶¶133-35.)

Kuo specifically teaches a POSA that methods of forming scaffolds “are known to the skilled artisan[s]” and cites to various references regarding fabricating the scaffold. (EX1018, [0040].) Kuo could not cite Huang2 because the application was filed before Huang2 was published. Further, as set forth above,

there would be more than a reasonable expectation of success in making this combination as both Huang<sup>2</sup> and Kuo successfully created scaffold of aligned fibers comprising collagen. (EX1003, §A.1.d.)

**B. Claim 2: “The method of claim 1, wherein the scaffold is in the form of one or more elongated sheets.”**

Claim 1 is obvious for the reasons expressed above in § X.A., *supra*, which are incorporated herein. Further, a POSA would understand that the electrospun fibers fabricated in Huang<sup>2</sup> would constitute a “sheet” within the meaning of claim 2. (EX1003, §VI.A.2.) In addition, Kuo discloses “a composition comprising: a porous scaffold *sheet* of fibrous material; and living cells deposited thereupon” as set forth in dependent claim 2, which covers at least one elongated sheet. (EX1018, [0007], [0020], [0022] (emphasis added.) For the reasons set forth above, a POSA would have been motivated with a reasonable expectation of success to use Huang<sup>2</sup>’s aligned fibers in scaffolds in the form of one or more elongated sheets as disclosed by Kuo. (See §X.A., *supra*.) Claim 2 is thus obvious over Huang<sup>2</sup> in view of Kuo.

**C. Claim 3: “The method of claim 1, wherein the scaffold is a composite of multiple layers of one or more sheets.”**

Claim 1 is obvious for the reasons expressed above in § X.A., *supra*, which are incorporated herein. In addition, and as set forth above, Kuo specifically discloses “a composition comprising: a porous scaffold sheet of fibrous material;

and living cells deposited thereupon” as set forth in dependent claim 3. (EX1018, [0007], [0020], [0022]; EX1003, §VI.A.3.) Further, Kuo also discloses that there can be multiple “sheets” in the scaffold, which can be arranged in any configuration: “A scaffold may be in a particular shape or form so as to influence or delimit a three-dimensional shape or form assumed by a population of proliferating cells. Such shapes or forms include, but are not limited to . . . sheets . . .” (EX1018, [0024].) “A scaffold can be held together into any shape and/or size to be used as a construct for tissue regeneration, enhancement, or repair of a desired tissue.” (EX1018, [0049].) “Scaffold sheets comprised of fibers with diameters of micrometer or nanometer or other dimension and with fibers that are oriented at random, aligned, etc. are produced by e.g., electrospinning.” (EX1018, [0034].) Indeed, in addition to the above, the use of multi-layered sheets for an implant was well within the level of skill of a POSA, having been used extensively in the scientific literature. *See e.g.*, Michael J. McClure, David G. Simpson, Gary L. Bowlin, *Tri-layered vascular grafts composed of polycaprolactone, elastin, collagen, and silk: Optimization of graft properties*, Journal of the Mechanical Behavior of Biomedical Materials, Volume 10, 2012, Pages 48-61 (EX1022). For the reasons set forth above, a POSA would have been motivated with a reasonable expectation of success to use Huang2’s aligned fibers in scaffolds in the form of

multiple layers of one or more sheets as disclosed by Kuo. (See § X.A., *supra*.)

Claim 3 is thus obvious over Huang2 in view of Kuo.

**D. Claim 4: “The method of claim 1, wherein the tissue defect is a the nerve defect.”**

Claim 1 is obvious for the reasons expressed above in § X.A., *supra*, which are incorporated herein. In addition, Kuo specifically discloses using an engineering scaffold to treat a nerve defect: “Another aspect described herein is a method for replacing or enhancing a tissue . . . . [T]he tissue is selected from the group consisting of a muscle, a nerve, a ligament, a tendon, or another tissue.” (EX1018, [0022], [0034].) According to Kuo, “scaffolds can be formed that replace/repair muscle, ligament, tendon, connective tissue, nerves, [and] nerve channels . . . .” (EX1018, [0052].) Accordingly, for the reasons set forth in § XI.A.4, *supra*, a POSA would have been motivated with a reasonable expectation of success to use Huang2’s aligned fibers to fabricate a scaffold to treat a nerve defect, as disclosed by Kuo. In particular, the structure and function of nerve tissue require that the cells grow in an aligned manner, and the native tissue are aligned. (EX1003, ¶¶133-35.) Indeed, Kuo teaches the desirability of using aligned fibers to mimic native tissues such as nerves. (EX1018, [0006], [0112]; EX1003, ¶¶133-35.) Further, a POSA would have known that nerves are composed of aligned fibers that induce cell growth along the axis of alignment, like Huang2’s scaffolds.

(EX1019, 3, 28; EX1005, 1794; EX1003, ¶¶133-35.) Claim 4 is thus obvious over Huang2 in view of Kuo. (EX1003, §VI.A.4.)

**E. Claim 5: “The method of claim 1, wherein the tissue defect is a the ligament defect.”**

Claim 1 is obvious for the reasons expressed above in § X.A., *supra*, which are incorporated herein. In addition, Kuo specifically discloses using an engineered scaffold to treat a ligament injury. (EX1018, [0006], [0034], [0067], [0112].) Accordingly, for the reasons set forth in § XI.A.4., *supra*, a POSA would have been motivated with a reasonable expectation of success to use Huang2’s aligned fibers to fabricate a scaffold to treat a ligament injury, as disclosed by Kuo. In particular, the structure and function of ligament tissue require that the cells grow in an aligned manner with strength along the axis of alignment and the native tissue are aligned, like the fibers in Huang2’s scaffolds. (EX1003, ¶¶133-34; EX1005, 1794.) Indeed, Kuo teaches the desirability of using aligned fibers to mimic native tissues such as ligament. (EX1018, [0006], [0112]; EX1003, ¶¶133-34.) Claim 5 is thus obvious over Huang2 in view of Kuo. (EX1003, §VI.A.5.)

**F. Claim 6: “The method of claim 1, wherein the tissue defect is a the tendon defect.”**

Claim 1 is obvious for the reasons expressed above in § X.A., *supra*, which are incorporated herein. In addition, Kuo specifically discloses using an engineering scaffold to treat a tendon injury. (EX1018, [0006], [0034], [0067],

[0112].) Accordingly, for the reasons set forth in § XI.A.4., *supra*, a POSA would have been motivated with a reasonable expectation of success to use Huang2's aligned fibers to fabricate a scaffold to treat a ligament injury, as disclosed by Kuo. In particular, the structure and function of tendon tissue require that the cells grow in an aligned manner with strength along the axis of alignment and the native tissue are aligned, like the fibers in Huang2's scaffolds. (EX1003, ¶¶133-34; EX1005, 1794.) Indeed, Kuo teaches the desirability of using aligned fibers to mimic native tissues such as tendon. (EX1018, [0006], [0112]; EX1003, ¶¶133-34.) Claim 5 is thus obvious over Huang2 in view of Kuo. (EX1003, §VI.A.6.)

**XI. GROUND 2: LEE ALONE OR IN VIEW OF KUO RENDERS CLAIMS 1-6 OBVIOUS UNDER 35 U.S.C. § 103**

Claims 1-6 of the '227 patent would have been obvious in view of Lee alone or when read in combination with Kuo. (EX1003, §VI.B.) Lee discloses the use of a scaffold as recited by claim 1 for the treatment of a muscle defect. It would have been the epitome of obviousness based on Lee alone for a POSA to use the scaffolds fabricated in Lee with aligned crosslinked collagen fibers to treat a tendon, ligament, or nerve defect. This is particularly the case if Lee is viewed in combination with Kuo.

**A. Claim 1**

**1. “A method of treating a tissue defect in a subject comprising implanting at the tissue defect a scaffold”**

Lee by itself discloses this element of the claim. (EX1003, §VI.B.1.a.) Lee discloses using an electrospun scaffold to treat a tissue defect, i.e., an injury to muscle tissue. Lee teaches that the reconstruction of skeletal muscle tissue due to a traumatic injury is difficult because of the lack of “functional muscle tissue substitutes.” (EX1011, [0003].) To solve this problem, Lee describes engineered muscle tissue, including “a *biodegradable scaffold comprising a plurality of fibers oriented along a longitudinal axis of the fibers*” and “methods of forming a biodegradable scaffold, including the steps of electrospinning a solution comprising a biodegradable scaffold material onto a grounded mandrel to form a plurality of fibers oriented along a longitudinal axis; and crosslinking said fibers to form the scaffold.” (EX1011, [0005]-[0006] (emphasis added).) Lee further states that treating a muscle injury includes reconstructing skeletal muscle tissue (e.g., where such tissue has been damaged or lost by, e.g., injury or disease) by *implanting an anisotropic scaffold* (with or without muscle cells) into a subject in need thereof. Scaffolds may be *implanted, e.g., at or adjacent to the site of injury*, and/or at another site in the body of a subject that would impart a benefit to the subject, as would be appreciated by one of skill in the art.” (EX1011, [0028] (emphasis added).)

**2. “a scaffold comprising crosslinked fibers comprising collagen”**

Lee describes these claim elements. (EX1003, §VI.B.1.b.) As mentioned above, Lee describes “a biodegradable scaffold comprising a plurality of fibers” and “crosslinking said fibers to form the scaffold.” (EX1011, [0005]-[0006].) Lee also teaches creating a scaffold that contains collagen, as required by this claim element, stating that they had electrospun a “blend of PCL and collagen with a ratio of 1:1 in weight.” (EX1011, [0063].) Lee specifically describes how the fabricated fibers were cross-linked, stating that the “electrospun PCL/collagen nanofiber meshes were cross linked under vapor of 2.5% glutaraldehyde solution for 6 hr to increase stability and strength of collagen.” (EX1011, [0063].) Accordingly, these elements of the claim are disclosed by Lee.

**3. “wherein a result of a fast Fourier transform (FFT) analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other”**

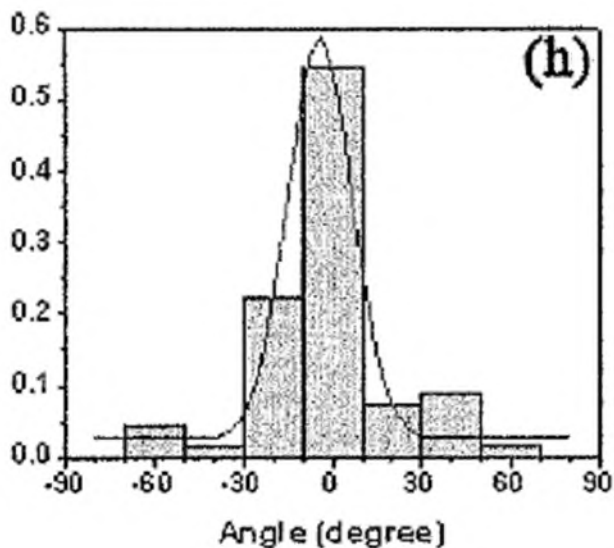
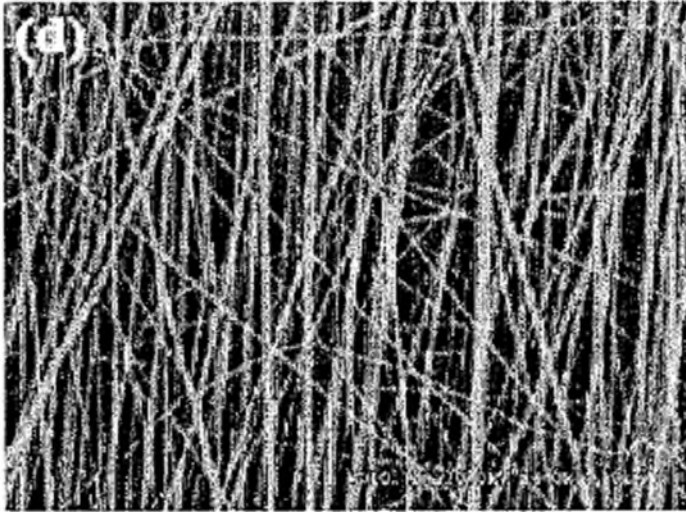
Lee by itself also discloses this element of the claim by describing aligned PCL/collagen fibers. (EX1003, §VI.B.1.c.) Indeed, in Lee, the investigators specifically investigated the impact of alignment and the orientation of electrospun PCL/collagen nanofibers on the performance and properties of electrospun scaffolds, finding that aligned fibers enhanced cell growth and organization on the scaffold. (EX1011, [0060], [0084-85], [0094-0095], *see* §IX.B., *supra*.)

Lee describes “PCL/collagen nanofiber meshes with different fiber angles [] produced by electrospinning at various rotation rates of 0 (static), 800, 1500, and 2350 rpm. Progressive increase in fiber orientation was observed as the rotation rate increased (FIG. 1 b). (EX1011, [0080].) In Lee, “fiber orientations were induced by electrospinning onto a collector at different rotation rates.” (Id., [0061].)

To determine fiber orientation in Lee, the “fiber morphologies of the electrospun PCL/collagen nanofiber meshes were examined by scanning electron microscopy (SEM; Model S-2260N, Hitachi Co., Ltd, Japan.).” (Id., [0065].) Further, “the SEM images were analyzed with UTHSCSA ImageTool 3.0 (Freeware provided by the University of Texas Heal Sciences Center, San Antonio, Tex., USA) to determine the average fiber diameters and *fiber orientations* within the nanofiber meshes . . . . In fiber angles of the nanofibers, histograms were plotted over the entire +90° to -90 ° range.” (Id., [0066] (emphasis added).)

Lee’s most aligned fibers comprising collagen are shown in Figure 1D and corresponding histogram Figure 1H. The below image analysis was done using Lee’s provisional, U.S. Provisional Patent App. No. 61/025,350, which discloses the same data, but with a clearer image. Indeed, the scaffold in both Lee and its provisional are the same. (*E.g., compare* EX1011, [0062]-[0095] (materials and

methods, results, discussion, conclusion) with EX1021, 14-24 (substantively identical); EX1003, ¶179.)



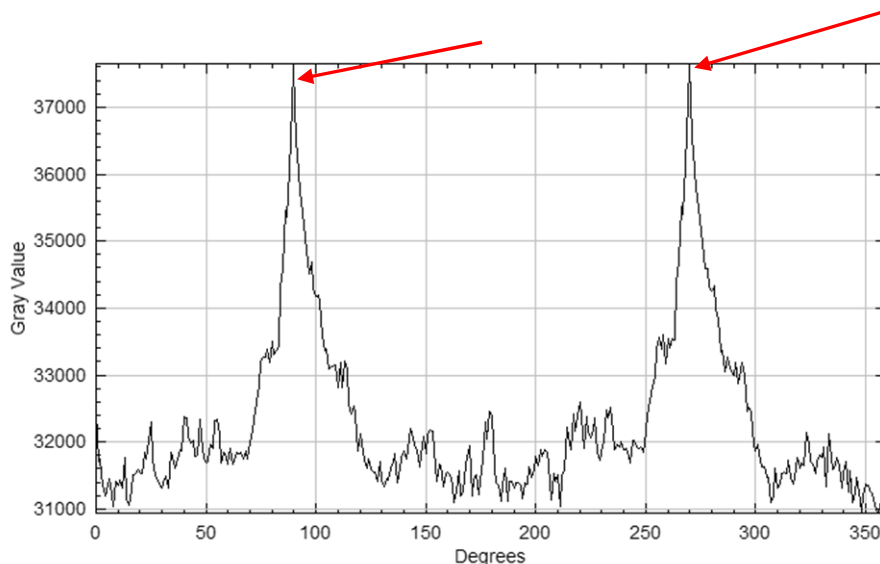
(EX1021, Figs. 1D., 1H.) The image analysis from Figures 1D and 1H show that Lee discloses highly aligned fibers. (EX1003, ¶¶179-85.)

Lee used freeware provided UTHSCSA provided by the University of Texas Heal Sciences Center, San Antonio, Tex., USA (ImageTool 3.0) to measure the

degree of alignment, A POSA, however, would know that the degree of alignment could also be determined using ImageJ software to run an “FFT analysis” on the images published in Lee. (EX1003, ¶181.) An FFT analysis also measures the degree of orientation of fibers and can be used on a published SEM image. (EX1003, ¶181.) This application of ImageJ software was well-known at the time of filing of Lee. (EX1013; EX1010; EX1003, ¶181.)

Thus, if a POSA wanted to perform an FFT analysis on the SEM image in Lee, a POSA could do so using the ImageJ software, and would know how to perform the straightforward analysis on the very SEM image of the electrospun fibers shown in Lee. (EX1003, ¶¶181-87.) This would show the fibers were oriented on the scaffold in Lee in an aligned manner.

To demonstrate this, Petitioners’ expert, Dr. Simpson, ran an FFT analysis on Lee’s Figure 1D. (EX1003, ¶¶183-85.)



(EX1003, ¶¶183-85.) The resulting graph shows clear adjacent major peaks at around 90° and 270°. (EX1003, ¶184.) These peaks are thus about 180° apart from each other (annotated in **red**)—thus confirming Lee’s many statements that he had obtained aligned collagen fibers. (EX1003, ¶184.) Indeed, Lee also performed tensile testing on the prepared electrospun fibers, which further confirms that Lee obtained aligned fibers. (EX1011, [0025], [0067], [0081]; EX1003, ¶186.) Accordingly, this element of claim is disclosed by Lee. Indeed, at the very least, this element would have been obvious in view of Lee alone as Ayres 2008 (EX1010) had been published for years and was an established tool that was well-within the routine skill of a POSA at the time. (EX1003, ¶187.) Thus, a POSA would have been motivated to confirm the alignment of Lee’s fibers with a well-known established tool. (EX1003, ¶187.) And a POSA would have more than a reasonable expectation of success of successfully running an FFT on Lee’s SEM images, as Dr. Simpson has demonstrated. (EX1003, ¶187.)

**4. “and applying the scaffold to the tissue defect to repair a tendon, a ligament or a nerve defect”**

While Lee discusses using his scaffolds of aligned fibers comprising collagen to repair a tissue injury, i.e., a muscle injury, Lee does not expressly disclose using his scaffolds to repair a tendon, ligament, or nerve defect. This claim element, however, would have been obvious in view of Lee alone. (EX1003, §VI.B.1.d.) It would have been well-understood by a POSA as of the effective

priority date of the '227 patent that the teaching of Lee of using a scaffold comprising cross-linked aligned collagen fibers to treat a muscle injury could also be used to treat a tendon or ligament injury given the similarities between the tissue thus rendering this claim element obvious. (EX1003, §VI.B.1.d.)

Moreover, it certainly would have been obvious when Lee is viewed in combination with Kuo, which expressly teaches using an engineered scaffold comprising cross-linked aligned collagen fibers to repair multiple tissue injuries, including, tendon, ligament, and nerve. (EX1018, [0005], [0022-23], [0052]; EX1003, §VI.B.1.d.)

A POSA would have had the necessary motivation to combine Lee and Kuo because both are in the same field of art, both seek to solve the same problems—using a bioengineered scaffolds containing crosslinked collagen fibers to treat a tissue injury—muscle in Lee, ligament and tendon in Kuo, and both teach that aligned fibers are desirable to promote cell growth. (See EX1011, [0003], [0005]-[0006], [0009], [0081], [0094]; EX1018, [0003-0006], [0052], [0058], [0067], [0112], [0113]; EX1003, ¶190.)

This is particularly so where the structure and function of tendon, ligament, and nerve tissue require that the cells grow in an aligned manner, and the native tissue are aligned. (EX1003, ¶¶194-96.) Indeed, Kuo teaches the desirability of using aligned fibers to mimic native tissues such as muscles, tendons, ligaments,

and nerves. (EX1018, [0006], [0112]; EX1003, ¶¶194-96.) A POSA would have been well aware of the concept of using scaffolds that mimic the structure and function of native tissues. (EX1018, [0006], [0034], [0112], EX1019, 27; EX1003, ¶¶194-96.) A POSA also would have known that muscle, tendons, and ligaments are comprised of aligned type 1 collagen and require strength along the axis of alignment, like Lee's scaffold demonstrated. (EX1019, 3, 32; EX1011, Figure 2, [0025], [0067], Claim 8; EX1003, ¶¶194-96.) Further, a POSA would have known that nerves are composed of aligned fibers that induce cell growth along the axis of alignment, like Huang2's scaffold demonstrated. (EX1019, 3, 28; EX1011, [0094]; EX1003, ¶¶194-96.)

Additionally, Kuo cites Lanza & Atala, *Methods of Tissue Engineering* Academic Press; 1st edition October 2001 for the proposition that appropriate growth conditions for cells "are well known in the art." Anthony Atala, one of the authors of this Tissue Engineering textbook, is the co-inventor of Lee. Accordingly, a POSA would have been motivated and able to use a scaffold comprising Lee's aligned fibers containing collagen, which are crosslinked, to treat a tendon, ligament, or nerve defect as taught by Kuo.

A POSA would have been able to do so using well-known established methods described in both Lee and Kuo to achieve predictable results with a reasonable expectation of success. (EX1003, ¶193.) This is particularly so as both

Lee and Kuo successfully created scaffolds containing fibers containing blends of collagen and PCL, and both Lee and Kuo reported obtaining aligned fibers.

(EX1003, §VI.B.1.d.)

**B. Claim 2: “The method of claim 1, wherein the scaffold is in the form of one or more elongated sheets.”**

Claim 1, upon which claim 2 depends, is obvious for the reasons expressed above in § XI.A., *supra*, which are incorporated herein. Further, a POSA would understand that the electrospun fibers fabricated in Lee would constitute a “sheet” within the meaning of claim 2. (EX1003, §VI.B.2.) In addition, Kuo discloses “a composition comprising: a porous scaffold *sheet* of fibrous material; and living cells deposited thereupon” as set forth in dependent claim 2, which covers at least one elongated sheet. (EX1018, [0007], [0020], [0022] (emphasis added.)

Accordingly, for the reasons set forth in §XI.A.4, *supra*, a POSA would have been motivated with a reasonable expectation of success to use Lee’s aligned fibers in scaffolds in the form of one or more elongated sheets as disclosed by Kuo. Claim 2 is thus obvious over Lee in view of Kuo.

**C. Claim 3: “The method of claim 1, wherein the scaffold is a composite of multiple layers of one or more sheets.”**

Claim 1, upon which claim 3 depends, is obvious for the reasons expressed above in § XI.A., *supra*, which are incorporated herein. Lee teaches the additional elements of this claim, disclosing that “a polymeric matrix can be attached to one

or more polymeric matrixes to form a multilayer polymeric matrix structure.”

(EX1011, [0056].) In addition, Kuo also discloses that there can be multiple “sheets” in the scaffold, which can be arranged in any configuration: “A scaffold may be in a particular shape or form so as to influence or delimit a three-dimensional shape or form assumed by a population of proliferating cells. Such shapes or forms include, but are not limited to . . . sheets . . . .” (EX1018, [0024].)

“A scaffold can be held together into any shape and/or size to be used as a construct for tissue regeneration, enhancement, or repair of a desired tissue.”

(EX1018, [0049].) “Scaffold sheets comprised of fibers with diameters of micrometer or nanometer or other dimension and with fibers that are oriented at random, aligned, etc. are produced by e.g., electrospinning.” (EX1018, [0034].)

Indeed, in addition to the above, the use of multi-layered sheets for an implant was well within the level of skill of a POSA, having been used extensively in the scientific literature. *See e.g.*, Michael J. McClure, David G. Simpson, Gary L. Bowlin, *Tri-layered vascular grafts composed of polycaprolactone, elastin, collagen, and silk: Optimization of graft properties*, Journal of the Mechanical Behavior of Biomedical Materials, Volume 10, 2012, Pages 48-61 (EX1022).

Accordingly, for the reasons set forth in § X.A.4, *supra*, a POSA would have been motivated with a reasonable expectation of success to use Lee’s aligned fibers in scaffolds in the form of multiple layers of one or more sheets as disclosed by Kuo

and as well understood by a POSA. Claim 3 is thus obvious over Lee in view of Kuo.

**D. Claim 4: “The method of claim 1, wherein the tissue defect is a the nerve defect.”**

Claim 1, upon which claim 4 depends, is obvious for the reasons expressed above in § XI.A., *supra*, which are incorporated herein. In addition, Kuo discloses the additional element of this claim, i.e. “where the tissue defect is a the nerve defect.” Kuo specifically discloses using an engineered scaffold to treat a nerve defect: “Another aspect described herein is a method for replacing or enhancing a tissue . . . . [T]he tissue is selected from the group consisting of a muscle, a nerve, a ligament, a tendon, or another tissue.” (EX1018, [0022], *see also* [0034].)

According to Kuo, “scaffolds can be formed that replace/repair muscle, ligament, tendon, connective tissue, nerves, [and] nerve channels . . . .” (EX1018, [0052].)

Accordingly, for the reasons set forth in § XI.A.4, *supra*, a POSA would have been motivated with a reasonable expectation of success to use Lee’s aligned fibers to fabricate a scaffold to treat a nerve defect, as disclosed by Kuo. In particular, the structure and function of nerve tissue require that the cells grow in an aligned manner, and the native tissue are aligned. (EX1003, ¶¶194-96.) Indeed, Kuo teaches the desirability of using aligned fibers to mimic native tissues such as nerves. (EX1018, [0006], [0112]; EX1003, ¶¶194-96.) Further, a POSA would have known that nerves are composed of aligned fibers that induce cell growth

along the axis of alignment, like Lee's scaffolds. (EX1019, 3, 28; EX1011, [0094]; EX1003, ¶¶194-96.) Claim 4 is thus obvious over Lee in view of Kuo. (EX1003, §VI.B.4.)

**E. Claim 5: “The method of claim 1, wherein the tissue defect is a the ligament defect.”**

Claim 1, upon which claim 5 depends, is obvious for the reasons expressed above in § XI.A., *supra*, which are incorporated herein. Further, Lee alone renders the additional element of this claim obvious, i.e. “where the tissue defect is a the ligament defect.” It would have been well-understood by a POSA as of the effective priority date of the '227 patent that the teaching of Lee of using a scaffold comprising cross-linked aligned collagen fibers to treat a muscle injury could also be used to treat a ligament injury given the similarities between the tissues thus rendering this claim element obvious. (EX1003, §VI.B.1.d.) Both muscle and ligament are naturally aligned and require strength along the axis of alignment. (*Id.*) Further, Kuo also discloses the additional element of this claim. Kuo specifically discloses using an engineered scaffold to treat a ligament injury. (EX1018, [0006], [0034], [0067], [0112].) Accordingly, for the reasons set forth in § XI.A.4., *supra*, a POSA would have been motivated with a reasonable expectation of success to use Lee's aligned fibers to fabricate a scaffold to treat a ligament injury, as disclosed by Kuo. This is particularly so where the structure and function of ligament tissue require that the cells grow in an aligned manner

with strength along the axis of alignment and the native tissue are aligned, like the fibers in Lee's scaffolds. (EX1003, ¶¶194-96; EX1011, Figure 2, [0025], [0067], Claim 8.) Indeed, Kuo teaches the desirability of using aligned fibers to mimic native tissues such as ligament. (EX1018, [0006], [0112]; EX1003, ¶¶194-96.) Claim 5 is thus obvious over Lee in view of Kuo. (EX1003, §VI.B.5.)

**F. Claim 6: “The method of claim 1, wherein the tissue defect is a the tendon defect.”**

Claim 1, upon which claim 6 depends, is obvious for the reasons expressed above in § XI.A., *supra*, which are incorporated herein. Further, Lee alone renders the additional element of this claim obvious, i.e. “where the tissue defect is a the tendon defect.” It would have been well-understood by a POSA as of the effective priority date of the '227 patent that the teaching of Lee of using a scaffold comprising cross-linked aligned collagen fibers to treat a muscle injury could also be used to treat a ligament injury given the similarities between the tissues thus rendering this claim element obvious. (EX1003, §VI.B.1.d.) Both muscle and ligament are naturally aligned and require strength along the axis of alignment. (*Id.*) In addition, Kuo also discloses the additional element of this claim. Kuo specifically discloses using an engineered scaffold to treat a tendon injury. (EX1018, [0006], [0034], [0067], [0112].) Accordingly, for the reasons set forth in § XI.A.4., *supra*, a POSA would have been motivated with a reasonable expectation of success to use Lee's aligned fibers to fabricate a scaffold to treat a

tendon injury, as disclosed by Kuo. In particular, the structure and function of tendon tissue require that the cells grow in an aligned manner, have strength along the axis of alignment, and the native tissue are aligned. (EX1003, ¶¶194-96.)

Indeed, Kuo teaches the desirability of using aligned fibers to mimic native tissues such as tendons. (EX1018, [0006], [0112]; EX1003, ¶¶194-96.) A POSA also would have also known that tendons are composed of aligned type 1 collagen and require strength along the axis of alignment, like the aligned fibers in Lee's scaffolds. (EX1019, 3, 32; EX1011, Figure 2, [0025], [0067], Claim 8; EX1003, ¶¶194-96.) Claim 6 is thus obvious over Lee in view of Kuo. (EX1003, §VI.B.6.)

## **XII. GROUND 3: HUANG2 ANTICIPATES CLAIMS 7 AND 8 UNDER 35 U.S.C. §102**

### **A. Claim 7**

#### **1. “A method of cell culture comprising placing cells on a scaffold comprising aligned fibers”**

Huang2 discloses this element of the claim. (EX1003, §VI.C.1.a.) Huang2 placed cells, fibroblasts, on a scaffold containing both aligned and unaligned fibers to determine how the alignment affects cell growth and behavior on the scaffold. (EX1005, 1791.) “Normal human dermal fibroblasts (NHDFs) were seeded on collagen-containing PCL nanofibrous matrices with either isotropic nanofiber arrangement (i.e., randomly collected nanofibers with no alignment, abbreviated as “Iso”) or anisotropic nanofiber arrangement (i.e., collected nanofibers with alignment, abbreviated as “Aniso”).” (*Id.*, 1792.)

**2. “wherein a result of a FFT analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other”**

Huang2 discloses this element of the claim for the reasons set forth in §X.A.3, *supra*. (EX1003, §VI.C.1.b.) In particular, as set forth above, Huang2 fabricated a scaffold containing “PCL/Coll nanofibers aligned along a single axis (Fig. 1B).” (EX1005, 1794; EX1003, §VI.C.1.b.). Huang2 ran an FFT and as typical in the field, reported the results out to 180°, which showed a single major peak at about 90°. (EX1003, ¶47, ¶237; EX1010, 609.) As such, and as explained above, because of the intrinsic symmetry of an FFT, Huang2’s FFT analysis would show a second major peak at around 270° (which is 180° from the 90° peak) if the scale were extended to 0°-360°. (EX1003, ¶237; EX1010, 609.) Thus, a POSA would know from the alignment of the fibers depicted in the image of Figure 1B and the major peak at around 90° in Figure 1C that the fibers are aligned, such that there would necessarily be a second peak about 180° apart at 270°. (EX1003, ¶237.) As also shown above, Dr. Simpson conducted his own FFT analysis of Figure 1B and reported data from 0° to 360°. (EX1003, ¶¶125-126, 241-42.) The graph generated from the FFT analysis performed by Dr. Simpson demonstrates that the aligned fibers have a major peak at about 90° and, because Dr. Simpson reported all the peaks through 360°, a second major peak at

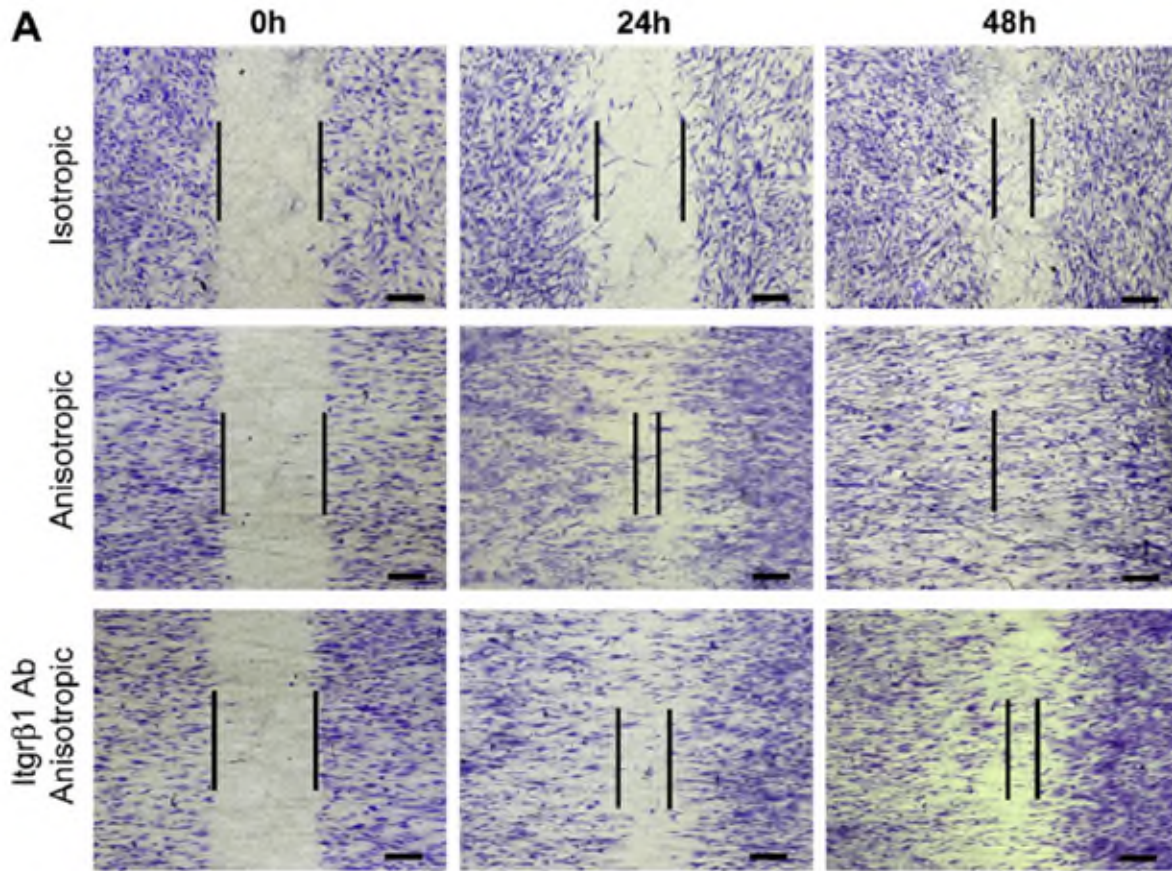
about 270°, which shows that the peaks are 180° apart as recited in claim 1.

(EX1003, ¶126, 242.)

**3. “and growing the cells in conditions suitable for the cell culture”**

Huang2 discloses this element of the claim as well. (EX1003, §VI.C.1.c.)

Huang2 teaches culturing fibroblasts under suitable conditions such that the cells grow. Huang2 discloses that “fibroblasts were seeded on the nanofibrous matrices at a density of  $5 \times 10^3$  cells/cm<sup>2</sup> and allowed to attach for 60 min before fully supplemented media was added. The cells were cultured on the isotropic or anisotropic nanofibrous matrices for up to 7 days.” (EX1005, 1792.) Huang2 further explains that “[i]n order to evaluate the effects of various fiber organizations (i.e., isotropic vs. anisotropic) on [normal human dermal fibroblast] migration, an in vitro wound healing assay was performed by culturing cells on various matrices with “wound gaps” created by an insert (Fig. 6A).” (*Id.*, 1796.) As seen in the figure below, Huang2 discloses culturing the NHDFs over a period of 48 hours and describes the differences between cell growth observed on anisotropic (aligned) and isotropic (randomly oriented) scaffolds. (EX1003, ¶247; *see also* EX1005, 1799, Figs. 2-7.)



Accordingly, Huang2 plainly discloses this element of the claim and indeed all the elements of claim 7 and thus anticipates the claim.

## B. Claim 8

For the reasons set forth in §§ XII.A.1-3, Huang2 discloses all the elements of claim 7. Claim 8 depends on claim 7 and further requires that “the cells are stem cells, adipose derived stem cells, dental pulp stem cells, *fibroblasts*, and/or dorsal root ganglia.” (Emphasis added.) Huang2 satisfies this claim element as well. As mentioned above, Huang2 specifically describes growing fibroblasts on the aligned collagen/PCL scaffold “fibroblasts were seeded on the nanofibrous

matrices at a density of  $5 \times 10^3$  cells/cm<sup>2</sup> and allowed to attach for 60 min before fully supplemented media was added. The cells were cultured on the isotropic or anisotropic nanofibrous matrices for up to 7 days.” (EX1005, 1792; *see also* §XII.A.3, *supra*.) Thus, Huang<sup>2</sup> discloses every element of this claim and anticipates it.

**XIII. DISCRETIONARY CONSIDERATIONS UNDER 35 U.S.C. §§ 314(a), 325(d) STRONGLY FAVOR INSTITUTION.**

**A. Fintiv Factors**

The proper application of the *Fintiv* factors favor institution and do *not* warrant discretionary denial under 35 U.S.C. § 314(a). Petitioners’ arguments are compelling, and the supporting evidence is substantial. That “alone demonstrates that the PTAB should not discretionarily deny institution under *Fintiv*.” (EX1024, 4-5.) Additionally, none of the factors justify denial:

**Factor 1:** Petitioners plan to seek a stay, and the district court case is in its infancy, making a stay likely. Indeed, a scheduling order has not even been entered in the district court litigation yet.

**Factor 2:** Given that a scheduling order has not even been issued yet, a final written decision will like precede trial. This is particularly so as the Eastern District of Virginia typically stay proceedings in light of a pending IPR petition.

**Factor 3:** Because no scheduling order has been entered in the district court litigation, significant work remains to be done in the case. Indeed, claim

construction, discovery, pre-trial motions, preparing for trial, the trial process, and posttrial motions all lie in the future.

**Factor 4:** Because of the early stage of the district court litigation, no invalidity contentions have been presented. Thus, there is no overlap that warrants non-institution.

**Factor 5:** The fact that the same parties are in both forums is typical and, under a “holistic view,” does not outweigh the systemic efficiency of institution. *Samsung Elecs. Co. Ltd. v. Dynamics Inc.*, IPR2020-00505, Paper 11 at 15 (Aug. 12, 2020).

**Factor 6:** The public interest strongly favors eliminating “bad patents.” *Thryv, Inc. v. Click-To-Call Techs.*, 140 S. Ct. 1367, 1374 (2020). Additionally, as discussed above, Petitioners’ arguments are compelling.

**B. 35 U.S.C. § 325(d)**

The grounds raised by this Petition are not the same or substantially the same as art or arguments raised during prosecution. Neither Huang<sup>2</sup>, Lee, or Kuo were before the Examiner during prosecution of the ’227 patent. Such “new, noncumulative prior art asserted in the Petition” strongly favors institution. *Oticon Medical v. Cochlear*, IPR2019-00975, Paper 15 at 20 (P.T.A.B. Oct. 16, 2019) (§§ II.B and II.C precedential). Accordingly, denial under 35 U.S.C. § 325(d) is not appropriate. See *Advanced Bionics, LLC v. MED-EL Elektromedizinische*

*Gerate GmbH*, IPR2019-01469, Paper 6 at 8-9 (P.T.A.B. Feb. 13, 2020)

(precedential).

Should Patent Owner attempt to analogize any previously considered art or arguments to those presented here, Petitioners reserve the right to respond, including by showing that the Patent Owner is incorrect, and that the Examiner erred in a manner material to the patentability of the Challenged Claims.

The Board should institute review because the merits are strong and the circumstances here do not support discretionary denial. Should Patent Owner raise any discretionary denial theory not addressed above, Petitioners reserve the right to respond before institution.

#### **XIV. NOTICE OF FEES PAID**

Fees are submitted herewith. If additional fees are due during the proceeding, the undersigned authorizes the Office to charge them to Deposit Account No. 50-1349.

#### **XV. CONCLUSION**

For the reasons above, Petitioners respectfully request institution of *inter partes* review and cancellation of claims 1-8 of the '227 patent as anticipated and/or obvious in view of the prior art.

Date: 12/4/2024

/David Feigenbaum/

**CERTIFICATE OF COMPLIANCE**

The undersigned hereby certifies that the foregoing **Petition for *Inter Partes* Review** contains 12940 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

/David Feigenbaum/

**CERTIFICATE OF SERVICE**

I hereby certify that on December 4, 2024, I caused a true and correct copy of the forgoing Petition for Inter Partes Review of U.S. Patent No. 11,318,227 to be served via express mail on the Patent owner at the correspondence address of record as listed on Patent Center.

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A courtesy copy was also sent via electronic mail to the Patent Owner's litigation counsel at the following addresses:

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Respectfully submitted,

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