

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

LIFENET HEALTH,
Patent Owner.

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

**PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 10,137,223
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§42.100 *et seq.***

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PETITIONERS' EXHIBIT LIST

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1001	U.S. Patent No. 10,137,223 to Francis et al. (“the ’223 patent”)
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1003	Declaration of David G. Simpson, Ph.D.
1004	CV of David G. Simpson, Ph.D.
1005	Huang et al., <i>The involvement of integrin $\beta 1$ 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)
1006	Kumbar et al., <i>Electrospun nanofiber scaffolds: engineering soft tissues</i> , Biomed. Mater. 3 (2008) (“Kumbar”)
1007	Reserved
1008	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”)
1009	U.S. Patent App. Pub. No. 2004/0037813 to Simpson et al. (“Simpson”)
1010	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”)
1011	Lee et al., U.S. Patent Application No. US 2010/0331980 A1, Pub. Date December 1, 2011 (“Lee”)
1012	Reserved
1013	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”)
1014	U.S. Pat. No. 5,514,378 to Mikos (“Mikos”)

1015	Jose et al, <i>Fabrication and Characterization of Aligned Nanofibrous PLGA/Collagen Blends as Bone Tissue Scaffolds</i> , 50 Polymer 3778-85 (2009) (“Jose”)
1016	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”)
1017	Shoulders & Raines, <i>Collagen Structure and Stability</i> , 78 Annu. Rev. Biochem. 929 (2009)
1018	Kuo et al., U.S. Patent Application No. US 2011/0293685 A1, Pub. Date Dec. 1, 2011 (“Kuo”)
1019	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)
1020	Declaration of Emma Xu
1021	U.S. Provisional Patent App. No. 61/0255,35 (“Lee Provisional”)
1022	Reserved
1023	Reserved
1024	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 https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_.pdf

I. INTRODUCTION

Embody, Inc. and Zimmer Biomet Holdings, Inc. (“Petitioners”) requests review of claims 1-12 of U.S. Patent No. 10,137,223 (“the ‘223 patent”), entitled “Aligned Fiber and Method of Use Thereof,” which issued on November 17, 2018, and is assigned to LifeNet Health (“Patent Owner”).

The ‘223 patent pertains to electrospinning, which is a technique that can be used to create electrospun fibers for the preparation of scaffolds that can repair injuries to tissue. There are many factors that impact the properties of the scaffolds formed from the electrospun fibers. One such property is how the fibers are oriented when collected, i.e., the fibers can either be aligned or randomly oriented. The degree of alignment can be measured by different techniques. One such technique uses a computer program analysis known as a fast Fourier transform or “FFT” analysis. Claim 1, the only independent claim of the ‘223 patent, recites a scaffold of electrospun fibers comprising collagen that appear mostly aligned such that they contain major peaks that are about 180° apart from each other as determined by FFT analysis.

However, as discussed in detail below, electrospinning fibers, the importance of alignment, and FFT analysis, were all well-known in the prior art. And indeed, the original claims of the ‘223 patent, which did *not* require collagen,

were *rejected* because the prior art plainly disclosed electrospun fibers that were aligned such that an FFT analysis showed major peaks that were 180° apart.

In response, the Applicant argued that the prior art relied on by the Examiner did *not* show that fibers comprising *collagen* were oriented in an aligned manner on the scaffold. Rather, according to the Applicant, those collagen fibers appeared to be unaligned. The Applicant further argued that the prior art methods of electrospinning were incapable of producing aligned collagen fibers. The Applicant thereafter amended *all* of the then pending claims to specifically require collagen, and the claims were allowed following this amendment.

But scaffolds where electrospun fibers comprising collagen were oriented in an aligned way were also described in the prior art. Indeed, such fibers show major peaks about 180° apart as measured using FFT. This prior art, however, was *not* before the Examiner during prosecution of the '223 patent. This prior art anticipates independent claim 1 of the '223 patent under 35 U.S.C. § 102.

Further, the additional limitations of the dependent claims add nothing novel or non-obvious in view of this prior art but merely include known materials or techniques that were also already well-known in the art to be used in scaffolds of electrospun fibers that comprise collagen. As shown in detail below, this prior art also anticipates and/or renders obvious the dependent claims of the '223 patent.

Accordingly, claims 1-12 of the '223 patent are either anticipated and/or obvious in view of the prior art not previously before the Examiner. *Inter partes* review is thus 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 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 '223 patent is the subject of the following civil action: *LifeNet Health v. Zimmer Biomet Holdings, Inc.*, Case No. 2:23-cv-00479 (E.D. Va.) filed August 23, 2023 (“Related Matter”). Petitioner Embody is a named defendant in the Related Matter. ZBH was dismissed from the action for lack of personal jurisdiction and venue, on September 25, 2024. (Docket No. 39.)

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III. CERTIFICATION OF GROUNDS FOR STANDING

The '223 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 identifies three grounds of unpatentability:

Ground	References	Claims	Basis
1.	Huang2	1-12	§102
2.	Huang2 in view of Kumbar	4	§103
3.	Lee	1-12	§102
4.	Lee	1-12	§103

V. TECHNICAL BACKGROUND

A. Electrospinning was a Proven Technique for Producing Nanofibers for use in Tissue Grafting

Electrospinning was a well-established method for producing nanofibers as of March 14, 2013, the earliest priority date alleged for the '223 patent. (*See* Kumbar, 1-2; EX1003, §§III.A-B.) It was—and is—valued for its reproducibility and scalability. (EX1006, 1-3; 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. (EX1009, [0156]; 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,

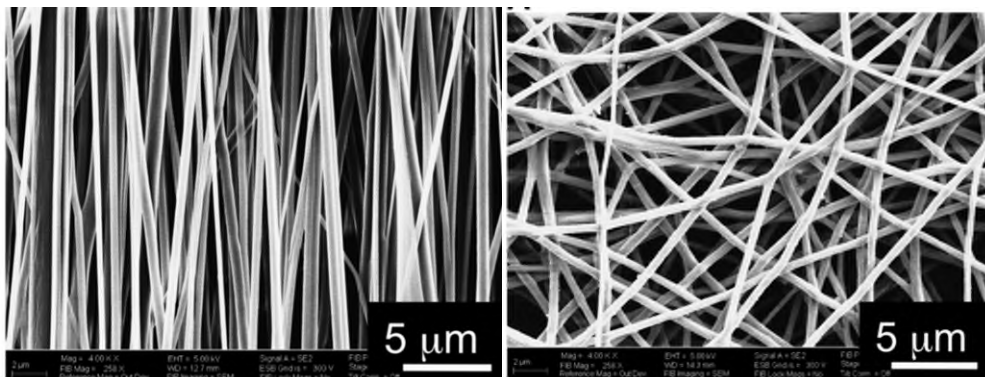
can alter the fibrous polymer scaffold's properties. (EX1006, 3-5; EX1013, 1; EX1003, ¶32.) For example, it was known that aligned fibers could be obtained using a rotating collector, among other methods. (EX1006, 3; EX1005, 1792; EX1009, [0176]; EX1003, ¶32.)

Electrospun nanofiber scaffolds share several key characteristics with the natural extracellular matrix ("ECM"). (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 for tissue regeneration and repair. (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; 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 discussed, the fibers obtained from electrospinning can either be aligned or randomly oriented as shown in the following images obtained from a scanning electron microscope:



(EX1005, 1793; EX1003, ¶¶38-45.) The image on the left shows fibers that are aligned, while the image on the right shows fibers that are randomly oriented. Increased 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 a graft that regenerates tissue. (EX1006, 7, 10; EX1003, §III.C.)

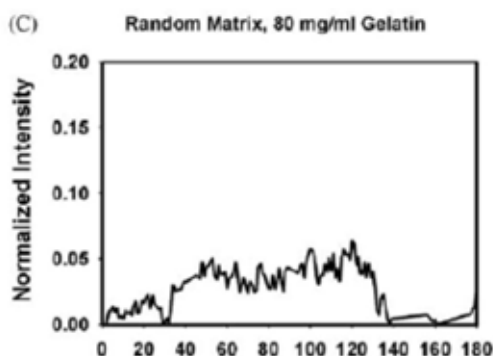
Incorporating collagen into fibrous scaffolds was also known to enhance their biological properties. (EX1010, 604; EX1006, 6; EX1018, [0112]; EX1003, §III.C.E.) Collagen, a polymer and the main component of the extracellular matrix (ECM), is ideal for biomedical applications because it is biocompatible, promotes cell attachment, and significantly boosts cell proliferation in fibrous scaffolds. (EX1006, 6-7; EX1009, [0004], [006], [0136]; *see also* EX1018, [0056], [0067]; EX1003, ¶53.) 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 mechanically weak. (EX1005, 1791; EX1003, ¶54.) 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, ¶54.) 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, ¶54.) 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, ¶54.)

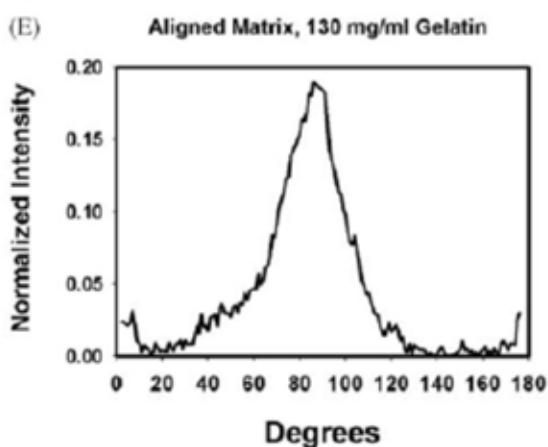
C. Determining Fiber Alignment Through FFT Analysis

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 '223 patent and is recited in its 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° (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, ¶46.) "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, ¶62.) 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 highly uniform fiber alignment. (EX1005, 1793; EX1016, 634; EX1003, ¶56.) 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. (EX1003, ¶57.)

VI. THE '223 PATENT

A. The Subject Matter of the '223 Patent

The '223 patent “relates to a scaffold comprising one or more electrospun fibers.” (EX1001, Abstract; EX1003, §IV.) The specification discloses that “electrospray/electrospinning techniques can be used to form particles and fibers as small as one nanometer in principal direction.” (*Id.*, 2:17-19.) The specification further notes that collagen is a material that can be used in creating fibers from electrospinning. (*Id.*, 14:51-55.) The specification does not assert that the named inventors were the first to use collagen as a material in electrospun fibers, and as discussed in the technical background section above, collagen had been widely used in the prior art for this purpose.

Further, the examples in the specification describe the material for the scaffold as either heart basement membrane (“HBM”) combined with polycaprolactone (“PCL”) or PLC alone. (*Id.*, 19:40-23:4 (Examples 1-4).) “FIG. 6 depicts aligned heart base [*sic*] membrane fiber scaffold that allow dorsal root ganglia attachment and outgrowth.” (*Id.*, 1:51-52.) “FIG. 7 depicts aligned placenta and heart base membrane fiber scaffolds that allow dorsal root ganglia attachment and outgrowth.” (*Id.*, 1:53-55.)

The specification states that for some embodiments, 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.*, 13:3-6.) According to the specification, “the major peaks . . . refer to peaks higher than the average peaks in the result.” (*Id.*, 13:6-7.)

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.*, 13:16-24.) 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, ¶46.) The analysis, as discussed above, need only be reported from 0° to 180°. (EX1003, ¶46.) This is because the peaks from 180° to 360° are repeats of the peaks from 0° to 180°. (EX1003, ¶46.) As stated by Ayres, which the ’223 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; *see also* EX1001, 13:16-26.)

FIG. 8 of the ’223 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.”

(EX1001, 1:56-57.) The specification further states that “[i]n some embodiments, FFT result of fibers described herein may have adjacent major peaks with about 180° apart from each other as shown in FIG. 8.” (*Id.*, 13:24-26.) Accordingly, aligned fibers in the prior art with major peaks corresponding to those shown in FIG.8A would anticipate the claims of the ’223 patent.

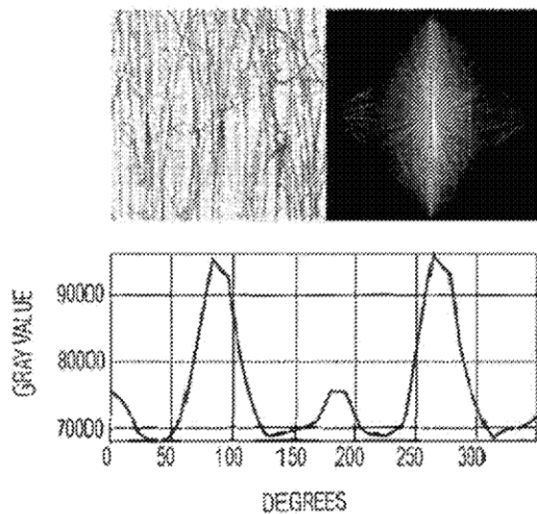


FIG. 8A

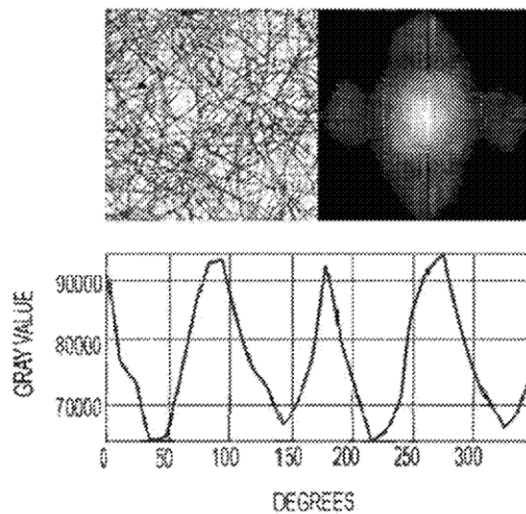


FIG. 8B

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, ¶64.) As noted above, and according to *Ayres*, which the specification incorporates for performing the FFT method, the graph in FIGS. 8A would only need to be reported through 180°. (EX1010, 609; EX1001, 13:16-26; EX1003, ¶64.) This is

because the peaks from 180° to 360° are repeats of the peaks from 0° to 180°.

(EX1003, ¶64.) Thus, even if FIG. 8A only reported data from 0° to 180°, a person of ordinary skill in the art (“POSA”) would have understood 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, ¶64.)

In contrast, the control sample in FIG. 8B shows peaks at about 0°, 90°, 180°, and 270°. (EX1003, ¶66.) These fibers do not appear aligned, as shown in FIG. 8B. (EX1003, ¶66.) Like above, and according to Ayres, the graph in 8B would only need to be reported to 180°.

B. The Claims

Claim 1 of the ’223 patent recites a scaffold of electrospun fibers that include collagen, wherein a FFT analysis shows that the fibers are aligned such that they have adjacent major peaks about 180° apart from each other. As discussed in detail below, this claim was amended during prosecution to require that the fibers contain collagen. Independent claim 1 is reproduced below.

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

The ’223 patent’s dependent claims depend either directly or indirectly from claim 1. These dependent claims also require aligned fibers as recited by claim 1

that comprise collagen and further cover scaffolds that have additional constituents and/or properties, as well as conventional methods for culturing cells on scaffolds. As shown below, these additional limitations were also well-known.

C. The Prosecution History

The '223 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, 2013.¹ However, 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 challenged claims could possibly claim priority to. Thus, Petitioners need not challenge the March 14, 2013, priority date unless necessary to do so in response to arguments made by the Patent Owner.

The '223 application received one office action rejection before allowance. The Examiner rejected claims 1 (corresponding to claim 1), 11 (corresponding to allowed claim 4), 12 (corresponding to allowed claim 5), and 17 (corresponding to allowed claim 6), as invalid as anticipated under 35 U.S.C. § 102(b) by Huang et

¹ In the Related Matter, LifeNet asserted that its invention date was March 14, 2013.

al., *Electrospun collagen-chitosan-TPU nanofibrous scaffolds for tissue engineered tubular grafts*, 82 Colloids and Surfaces B: Biointerfaces 307-315 (2011) (hereinafter referred to as “Huang1”). The Examiner stated that “Huang discloses a scaffold comprising one or more electrospun fibers” where the “[a]ligned nanofibrous scaffolds” were “[b]ased on collagen, chitosan, thermoplastic polyurethane (TPU) blends.” (Ex. 1002, 210.) The Examiner explained that these blended fibers “[w]ere electrospun to mimic the componential and structural aspects of the native extracellular matrix, while an optimal proportion was found to keep the balance between biocompatibility and mechanical strength.” (*Id.*, 210-211.) The Examiner further stated that “a fast Fourier transform (FFT) analysis result of the fibers have adjacent major peaks with about 180° apart from each other (Fig. 4E: pg. 309, Col. 2, two peaks at 175° and 355° (180° apart)).” (*Id.*, 211.) The Examiner further noted that Huang1 discloses “[t]hat the scaffold has an average porosity from about 60% to about 90% (Table 1).” (*Id.*)

The Applicant responded to the 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*.” (*Id.*, 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. Thus, the Applicant stated that based on this amendment, “[pending] claims 1, 11, 12, and 17 should not be rejected again as anticipated by Huang.” (*Id.*)

The Examiner further rejected pending claims 1, 5, 6, 11-12, 17, 19, 20-22 (corresponding to issued claims 1-10) as obvious under 35 U.S.C. § 103(a) by U.S. Patent App. Pub. No. 2004/0037813 (“Simpson”). (EX1002, 211.)² The Examiner explained that “Simpson beneficially teaches a scaffold comprising one or more electrospun fibers” and that “Simpson teaches that the secondary structure of collagen is not modified in the process of making the scaffold, as shown by Fourier transform infrared spectroscopy.” (*Id.*) The Examiner thus rejected these pending claims because “it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a scaffold comprising one or more electrospun fibers based upon the beneficial teachings provided by Simpson,” and that “[f]rom the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.” (*Id.*, 213.)

² This is the also the same Dr. Simpson who has filed a declaration supporting this petition.

The Applicant overcame the obviousness rejection based on Simpson by arguing that the scaffold in Simpson and Huang¹ was prepared using a rotating cylindrical collector, while the apparatus in the claimed invention uses a rotating, rod-shaped electrode to arrive at the claimed fiber alignment. Since, according to the Applicant, Huang¹ demonstrated that using a cylindrical collector to prepare electrospun fibers did not result in the claimed fiber alignment, a skilled artisan would not look to Simpson to arrive at the claimed fiber alignment as Simpson also uses the same rotating cylindrical collector. (*Id.*, 238-239.) Thus, a POSA “would not have expected to obtain the claimed fiber alignment” following the Simpson reference. (*Id.*) Accordingly, based on the Applicant’s amendment requiring collagen, the claims of the ’223 patent were allowed. (*Id.*, 247.)

VII. LEVEL OF ORDINARY SKILL IN THE ART

A POSA relevant to the ’223 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/performing FFT 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 '223 patent to describe the methods of performing the FFT analysis required by the claims of the '223 patent. (EX1003, ¶61.) 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. To the extent the Patent Owner identifies terms for construction, Petitioners reserve the right to respond.

IX. SUMMARY OF THE ASSERTED PRIOR ART

A. Huang et al., *The Involvement of Integrin β 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”)

The Huang reference relied on in the grounds below (“Huang2”) published online on December 2, 2011, which is more than a year before the earliest potential priority date of the '223 patent, which is March 14, 2013, and is prior art under at least Pre-AIA 35 U.S.C. § 102(b).³ Huang2 is a different prior art reference from a

³ 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. (EX1020, ¶11) Further, a hard copy of Huang2 obtained from the

different research group than the Huang reference (referred to as “Huang1”) that was cited during prosecution of the ’223 patent. (*See*, §VI.C., *supra*.)⁴ Huang2 was not cited during prosecution of the ’223 patent.

Huang2 studies fibers comprising collagen and sought to examine the effect of aligned fibers compared to non-aligned fibers on the attachment and growths of normal human dermal fibroblasts (“NHDFs”), including fibroblast-to-myofibroblast differentiation. (EX1005, 1797; EX1003, §V.A.) Huang2 sought to “understand how various nanofibrous matrices regulate skin cell behaviors and intracellular signaling pathways.” (EX1005, 1791 (Abstract).) To do this, Huang2 discusses creating scaffolds of “stable” collagen blended fibers for engineering skin grafts. (EX1005, 1791-92.) In Huang2’s study, “the phenotypic expressions of normal human dermal fibroblasts (NHDFs) on collagen-containing nanofibrous matrices with either isotropic (i.e., fibers collected randomly with *no alignment*) or

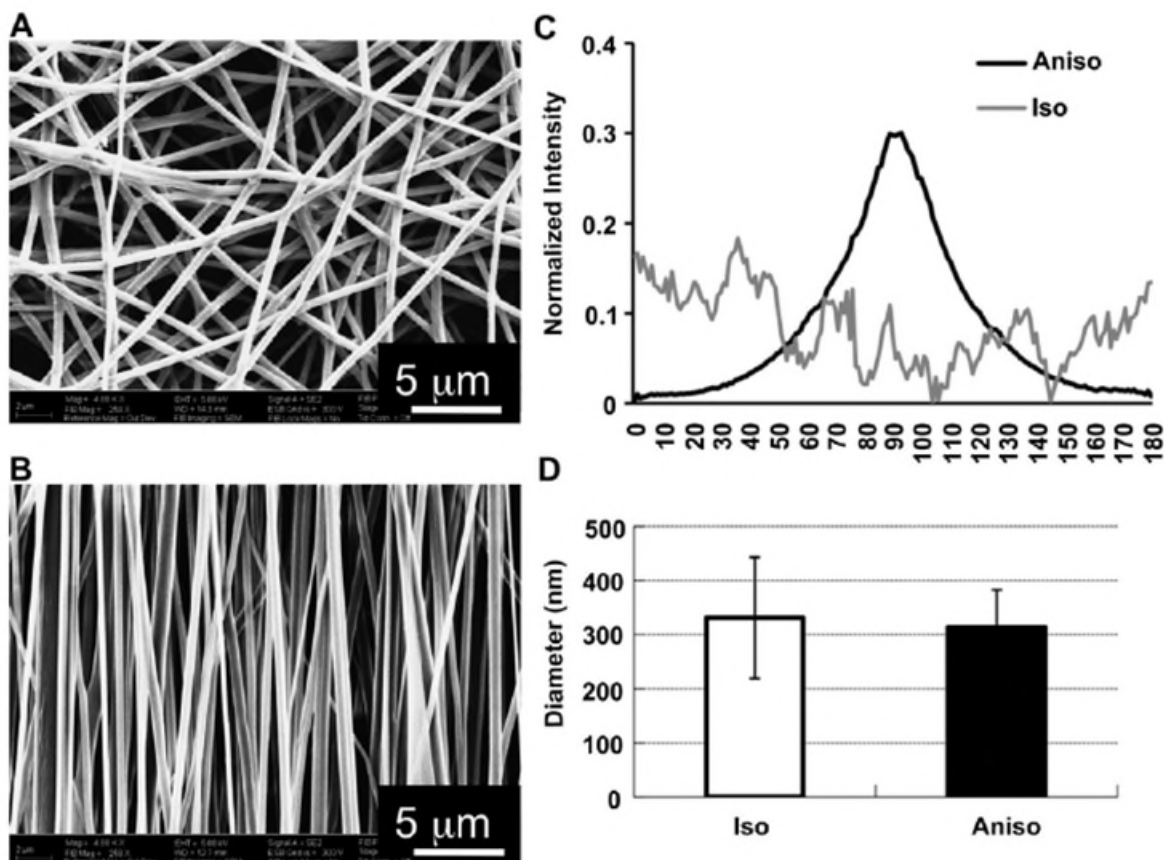
National Library of Medicine, has a date stamp, indicating it received a copy of Huang2 on February 21, 2012. (EX1005, PDF p. 1.)

⁴ As discussed above, (*see* §VI.C, *supra*), the Applicant argued during prosecution that the Huang1 did not disclose aligned fibers comprising collagen. The Applicant thus amended the claims to require collagen.

anisotropic (i.e., fiber collected with *alignment*) fiber organizations were studied . . .” (EX1005, 1791 (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 (aligned) nanofibrous matrices comprising collagen, likely due to the impact of the alignment on the integrin $\beta 1$ signaling pathway. (EX1005, 1797, 1799.)

Huang2 further discloses the importance of collagen in electrospinning fibers in tissue engineering. According to Huang2, “[c]ollagen fibrils, a major ECM component known for their mechanical contribution to skin integrity, provide an interactive 3D microenvironment to skin cells and regulate their behaviors via cell-matrix interactions.” (EX1005, 1791.) Huang2’s fibers comprised both PCL and collagen because collagen can be unstable. (*Id.*) Additionally, Huang2 discloses that “fibroblasts showed preferred adhesion on such collagen-containing nanofibers, comparable to pure collagen.” (EX1005, 1791-1792.) Specifically, “[n]anofibrous matrices of PCL and Collagen at a weight ratio of 3:1. . . were fabricated using electrospinning previously described.” (EX1005, 1792.)

The SEM images of the fibers comprising collagen oriented in Huang2's scaffolds are shown in Figure 1:



These images show the anisotropic (aligned) fiber sample (EX1005, 1793 (Figure 1B)) and the isotropic (non-aligned) sample (Figure 1A). (EX1005, 1793.)

To determine and show the alignment of the fibers used in the scaffolds, Huang2 also performed FFT analyses. The FFT analysis graph is reported at Figure 1C. (EX1005, 1793.) 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, ¶77.) No other major peaks would be present between 180° and 360° degrees for the Aniso (aligned) sample. (EX1003, ¶77.) 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, ¶77.) For the Iso sample, the FFT readout does *not* show a single major peak between 0° and 180° . (EX1003, ¶77.) Accordingly, the Iso (non-aligned) sample does not have major peaks 180° apart, which would be expected for an unaligned sample.

Finally, in discussing the importance of tissue engineering skin grafts, Huang2 teaches that “[t]o better support and facilitate skin cells to form skin-like tissues, it is necessary for the temporary scaffolds not only to provide a surface for the cells to reside, but also to define a cell-friendly microenvironment that maximally recaptures the native extracellular matrix (ECM). In this regard, electrospun nanofibrous matrices characterized by ultrafine continuous nanoscale fibers, high surface-to-volume-ratio, high porosity and variable pore size distribution have great potential to mimic the skin ECM in both morphology and composition.” (EX1005, 1791.) Huang2 cites to Kumbar, discussed below, to support this point.

B. Kumbar et al., *Electrospun Nanofiber Scaffolds: Engineering Soft Tissues*, Biomed Master 3 (2008)

Kumbar published on August 8, 2008, and is prior art under at least pre-AIA 35 U.S.C. § 102(b). Kumbar was not disclosed during prosecution of the '223 patent. As discussed above, Huang² relies on Kumbar in its discussion of the desirable properties of electrospun scaffolds. (EX1005, 1791.)

Kumbar describes research efforts in “designing nanofiber matrices as scaffolds in the regeneration of various soft tissues including skin, blood vessel, tendon/ligament, cardiac patch, nerve and skeletal muscle.” (EX1006, 1 (Abstract); EX1003, §V.B.) Kumbar notes that “electrospun nanofiber matrices have gained a lot of attention, and are being explored as scaffolds in tissue engineering due to their properties that can modulate cellular behavior.” (EX1006, 1 (Abstract).) In preparing the electrospun fibers, Kumbar discloses the importance of using collagen, explaining that “[c]ollagen nanofibers play a dominant role in maintaining the biological and structural integrity of various tissues and organs, including bone, skin, tendon, blood vessels and cartilage.” (*Id.*, 7.)

Kumbar also discloses desirable mechanical properties of scaffolds in tissue engineering. According to Kumbar, these properties are important “to provide cells with the necessary chemical cues and a more *in vivo* like environment” for use “in the regeneration of various soft tissues including skin[.]” (EX1006, 1

(Abstract).) Kumbar describes that “[f]iber alignment in nanofiber matrices significantly improves the mechanical properties.” (*Id.*, 6.)

Kumbar also explains that “[n]anofiber matrices as tissue engineering scaffolds need to have interconnected highly porous structures to facilitate cellular migration and transport of nutrients, and metabolic wastes to allow the formation of new tissue.” (EX1006, 6.) With respect to “[e]lectrospun nanofiber skin grafts,” Kumbar describes scaffolds of collagen nanofibers having a porosity of 71% to 89%, depending on the degree of crosslinking. (*Id.*, 7.)

**C. Lee et al., U.S. Patent Application No. US 2010/0331980 A1,
Aligned Scaffolding System For Skeletal Muscle Regeneration,
Pub. Date December 1, 2011**

Lee is US2010/0331980 A1, which published on December 30, 2010, and is prior art under at least Pre-AIA 35 U.S.C. § 102(b). Lee was not cited as prior art during the prosecution of the ’223 patent.

Lee teaches that the reconstruction of skeletal muscle tissue due to a traumatic injury is difficult because of “the lack of available functional muscle tissue substitutes.” (EX1011, [0003]; EX1003, §V.C.) 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].) Lee explains that its “[s]caffold’ refers to an array of natural or synthetic matrix molecules to which cells or fibers can attach,” which may include various components and molecules. (*Id.*, [0044].)

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 obtained Type 1 collagen and electrospun nanofiber meshes “using a blend of PCL and collagen with a ratio of 1:1 in weight.” (EX1011, [0062]-[0063].) Lee explains that “PCL-collagen composite scaffolds according to some embodiments have preferable biomechanical properties, e.g., yield tensile strength, elasticity and compliance.” (EX1011, [0052].) Lee teaches that when PCL and collagen are used together, “the mesh can be improved biocompatibility, mechanical properties, and processability,” and further explains that “in some embodiments the biomechanical properties of PCL-collagen scaffolds are similar to that of native tissue.” (*Id.*)

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, [91].) Lee discovered that “[f]iber alignment had a profound effect on the mechanical properties of electrospun PCL/collagen nanofiber meshes,” including increased tensile strength for the aligned nanofiber meshes. (EX1011, [0081].)

Lee explains that the aligned fibers aided in cell growth—“[t]he myotubes that formed on the oriented nanofiber meshes showed unidirectionally organized myotubes that are consistently aligned along the longitudinal axis of nanofibers, which is in contrast to the randomly oriented nanofiber meshes (FIGS. 5c, f).” (EX1011, [0084].) While the “myotubes formed on the randomly oriented nanofiber meshes . . . did not show a global cellular organization,” Lee states that the “myotubes on the aligned nanofiber meshes organized within close proximity to the direction of the nanofiber direction and formed globally aligned myotubes (FIG. 6d).” (EX1011, [0085].) Lee concludes that “[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].)

X. GROUND 1: ANTICIPATION IN VIEW OF HUANG2

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

Huang2 discloses all the elements of this claim as arranged in the claim.

(EX1003, §VI.A.1.)

1. “A scaffold comprising”

Huang2 discloses this element of the claim. (EX1003, §VI.A.1.a.) The use of scaffolds made from electrospun fibers were well-known in the prior art, as shown during prosecution of the '223 patent. In this regard, Huang2 discloses “scaffolds [that] not only . . . provide a surface for cells to reside, but also . . . define a cell-friendly microenvironment that maximally recaptures the native extracellular matrix (ECM).” (EX1005, 1791.) Huang2’s scaffolds, which comprise “nanofibrous matrices of PCL and Collagen” of anisotropic (aligned) nanofibers, are formed by electrospinning a solution of polycaprolactone (PCL) and collagen on a rotating mandrel. (EX1005, 1792; EX1003, §VI.A.1.a.) This claim element is plainly disclosed by Huang2.

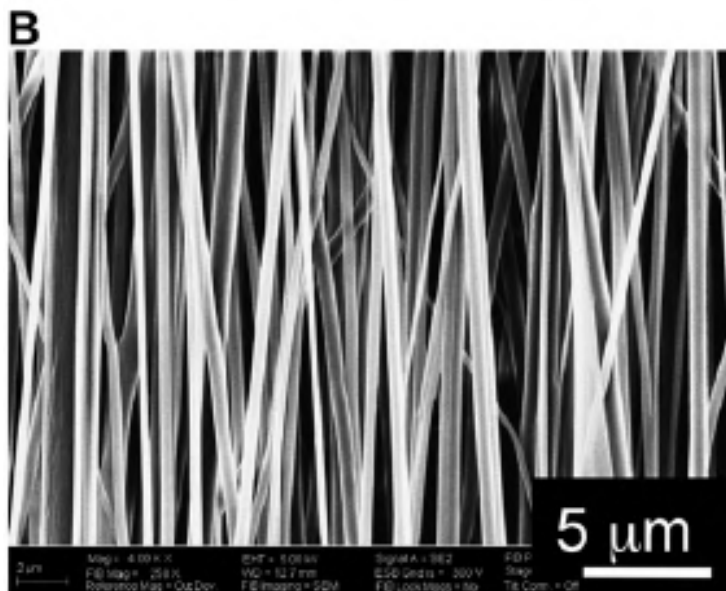
2. “one or more electrospun fibers comprising collagen”

Huang2 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

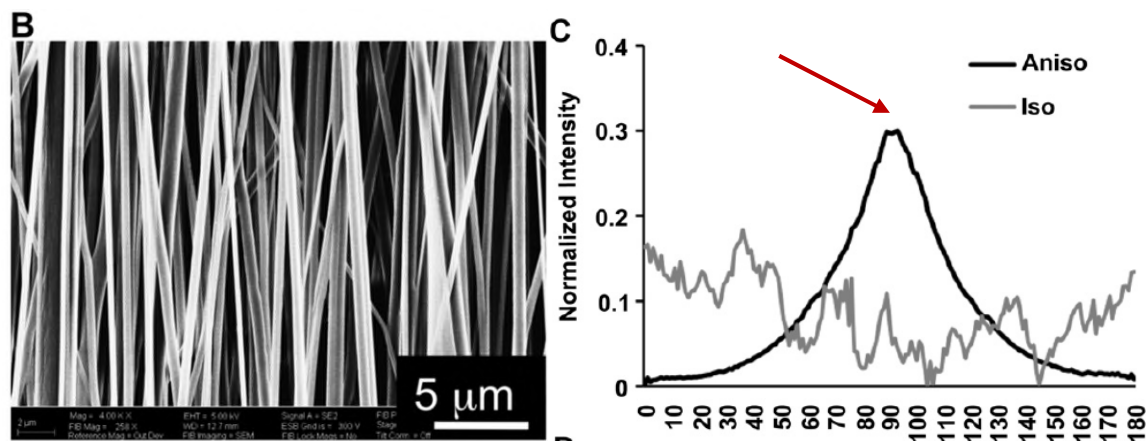
Collagen” from an “8% (w/v) solution of 3:1 PCL/Coll” with an electrospinning device. (EX1005, 1792.) Huang2 further explains that “[e]lectrospinning a blend solution of collagen and polycaprolactone (PCL) . . . can yield rather stable nanofibers.” (*Id.*, 1791.) This claim element is plainly disclosed by Huang2.

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

Huang2 discloses this element of the claim. (EX1003, §VI.A.1.c.) Huang2 describes PCL/collagen nanofibers that are visually highly aligned with major peaks that are about 180° apart by FFT analysis. Huang2 Figure 1B (below) is described as having “anisotropic” fibers, which as set forth above, means that the figure describes “collected nanofibers with alignment.” (EX1005, 1792-93, Fig. 1B.)



Huang2 itself states that they obtained fibers “aligned in the same direction.” (EX1005, 1794.) And Huang2 further confirmed the alignment of its anisotropic PCL/Coll fiber through the use of FFT analysis, stating that “[t]o better analyze the fiber alignment, an FFT analysis 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 ’223 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°:



(EX1005, 1793 (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, §VI.A.1.c.) 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.*, 1794 (emphasis added).)

As typical in the field, and as taught by Ayres, Figure 1C reports its results out to 180°. (EX1005, 1793; EX1003, §§III.D, VI.A.1.c.; EX1010, 609.) As such, and as explained above, 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°. (*Id.*, ¶106; 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 be a second peak about 180° apart at 270°. (EX1003, ¶106.)

Finally, Dr. Simpson conducted his own analysis of Figure 1B using the FFT analysis published in his papers and described in Huang2 and the ’223 patent and reported data from 0° to 360°. (EX1003, ¶¶110-111.)

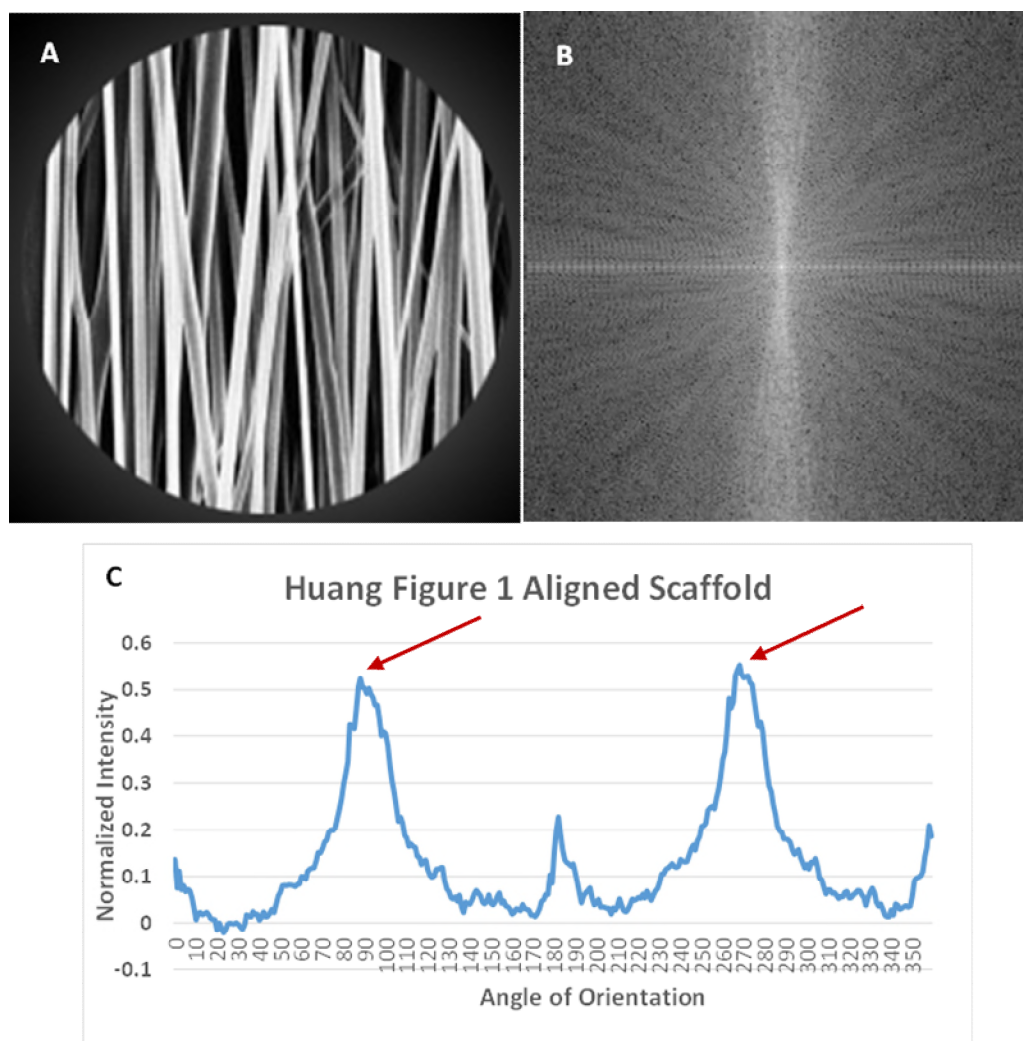


Figure 2. (A) Figure 1 from Huang aligned scaffold cropped and masked for 2DFFT. (B) 2DFFT spectrum of aligned scaffold, the image has been rotated to correct for the rotation intrinsic to the FFT analysis. (c) Normalized intensity values for aligned scaffold 0-360 degrees.

The graph generated from the FFT analysis performed by Dr. Simpson demonstrates that the aligned fibers in Huang2 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, ¶¶110-111.) The major peaks at about 90° and 270° are annotated with

red arrows). (EX1003, ¶¶110-111.) Indeed, Huang2 also performed materials testing on the prepared electrospun fibers, which further confirms that Huang2 obtained aligned fibers. (EX1005, 1794.)

Accordingly, this element of claim 1, and indeed all the elements of the claim, are plainly disclosed by Huang2, and Huang2 thus anticipates this claim.

B. Claim 2: “The scaffold according to claim 1, wherein the fibers comprise type I collagen in its native triple helical structure.”

Huang2 discloses all the elements of this claim as arranged in the claim. (EX1003, §VI.A.2.) As discussed in §X.A., *supra.*, Huang2 discloses all the elements of claim 1. Huang2 further discloses electrospinning PCL and “type I collagen” into fibers, as called for by claim 2. (EX1005, 1792.)

Huang2 also discloses the “native triple helical structure” element of the claim. Huang2 discloses that “type I collagen (Coll) was obtained from Elastin Products Inc.” (*Id.*) Type I collagen was well-known and generally understood in the art to have a triple-helical form when it is in a monomer, as well as when it is in a polymer. (EX1017, 1, 9; EX1003, ¶117.) A POSA would have understood that, if the type 1 collagen purchased from a supplier were denatured and/or fragmented (i.e., not in a triple helix) it would be sold as “gelatin,” not “collagen.” (EX1003, ¶117.) In addition, Huang2 discloses that the 3:1 ratio of PCL/Collagen was prepared by dissolving PCL and collagen in 1,1,1,3,3,3-hexafluoro-2-propanol or “HFIP.” (EX1005, 1792.) HFIP was known to stabilize collagen’s triple helix

structure. (EX1015, 3782.) Indeed, the prior art demonstrated that collagen purchased from Elastin Products maintained its native triple helical structure when using HFIP as the solvent. (EX1015, 2778-79, 3782.) HFIP is also the same solvent used in the '223 patent. (EX1001, 19:40-55 (example 1), 22:1-23 (example 2), 22:25-48 (example 3), 22:50-23:4 (example 4).) Accordingly, Huang2 plainly discloses all the elements of claim 2 and anticipates this claim.

C. Claim 3: “The scaffold according to claim 1, wherein the fiber has less than about 8 wt % residual calcium.”

Huang2 discloses all the elements of this claim as arranged in the claim. (EX1003, §VI.A.3.) As discussed in §X.A., *supra*, Huang2 discloses all the elements of claim 1. Further, Huang2 describes the materials used to prepare the nanofibers and does not indicate any calcium was used. (EX1003, ¶121.) In particular, the 3:1 ratio of PCL/Coll was prepared by dissolving PCL and collagen in 1,1,1,3,3,3-hexafluoro-2-propanol or “HFIP.” (EX1005, 1792.) Huang2 did not “incorporate” or otherwise use calcium in the production of these fibers. (EX1003, §VI.A.3.; EX1001, 11:2-4.) Thus, the 3:1 PCL/Coll electrospun nanofibers used in Huang2 would contain less than about 8 wt % residual calcium. (EX1003, §VI.A.3.) Accordingly, Huang2 plainly discloses all the elements of claim 3 and anticipates this claim.

D. Claim 4: “The scaffold according to claim 1, wherein the scaffold has an average porosity from about 60% to about 90%.”

Huang2 discloses all the elements of this claim as arranged in the claim.

(EX1003, §VI.A.4.) As discussed in §X.A., *supra*., Huang2 discloses all the elements of claim 1. Further, Huang2 explains that a goal of tissue-engineered skin grafts is to “define a cell-friendly microenvironment that maximally recaptures the native extracellular matrix (ECM).” (EX1005, 1791.) Huang2 further explains that electrospun scaffolds with a “*high porosity*” have the best “potential to mimic the skin ECM in both morphology and composition.” (EX1005, 1791 (Introduction) (emphasis added).) A POSA would understand that “high porosity” would include percentages of porosity that are within the range of 60% to 90% porosity as recited by claim 4. (EX1003, §VI.A.4.) This understanding of how a POSA would view “high porosity” is further confirmed by Kumbar, which Huang2 specifically cites as support for this point. (EX1005, 1791, 1799.) With respect to “[e]lectrospun nanofiber skin grafts,” Kumbar, a review article summarizing what a POSA would know (EX1003, §VI.A.4), also discusses the benefits of “high porosity” and describes scaffolds of collagen nanofibers having a porosity of 71% to 89%, depending on the degree of crosslinking. (EX1006, 1, 6-7, 12.) Accordingly, Huang2 discloses all the elements of claim 4 and anticipates this claim.

- E. Claim 5: “The scaffold according to claim 1, wherein the scaffold comprises collagen type I, bone matrix, adipose extracellular matrix, heart basement membrane extract, heart basement membrane extracellular matrix, placenta basement membrane extract, placenta basement membrane extracellular matrix, brain-derived extracellular matrix, polycaprolactone, an accessory polymer, or the mixture thereof.”**

Huang2 discloses all the required elements necessary to anticipate this claim.

(EX1003, §VI.A.5.) As discussed in §X.A., *supra.*, Huang2 discloses all the elements of claim 1. Huang2 further discloses that the prepared scaffolds comprise at least collagen type I, polycaprolactone, and the mixture thereof. For example, Huang2 discloses “[p]oly (epsilon-caprolactone) (PCL, Mw=80,000) . . . and type I collagen (Coll)” and fabrication of “[n]anofibrous matrices of PCL and Collagen.” (EX1005, 1792.) The fibers in the scaffold are also aligned. (See §X.A.3., *supra.*)

Huang2 also discloses the “accessory polymer” element of the claim. As mentioned above, the ’223 patent describes that an “accessory polymer” affects the “physical, chemical, and/or biological properties” of the scaffold, such as “tensile strength, hydrophilicity, biocompatibility,” and specifically teaches that the use of polycaprolactone or “PCL” as an accessory polymer. (EX1001, 12:8-14.) Huang2 likewise discloses the use of polycaprolactone or “PCL” to improve the stability and mechanical properties of the fibers, stating that “[e]lectrospinning a blend solution of collagen and polycaprolactone (PCL), a biocompatible and biodegradable synthetic polyester, can yield rather stable nanofibers,” thereby

avoiding drawbacks of pure collagen fibers. (*Id.*, 1791-92 (observing that pure collagen fibers degrade rapidly and have poor mechanical properties).) Huang2 thus discloses the use of an “accessory polymer” as called for by claim 5.

(EX1003, §VI.A.5.) Accordingly, Huang2 anticipates this claim.

F. Claim 6: “The scaffold according to claim 5, wherein the accessory polymer is selected from the group consisting of polycaprolactone, poly(glycolic acid), poly(lactic acid), polydioxanone, poly(lactide-co-glycolide) copolymers, polyesters polysaccharides, polyhydroxyalkanoates, starch, polylactic acid, cellulose, proteins, agar, silks, alginate, collagen / gelatin, carrageenan, elastin, pectin, resilin, konjac, adhesives, gums, polyamino acids, polysaccharides, soy, zein, wheat gluten, casein, chitin / chitosan, serum albumin, hyaluronic acid, lipids / surfactants, xanthan, acetoglycerides, waxes, surfactants, dextran, emulsan, gelatin, polyphenols, levan, lignin, curd, inulin, tannin, polygalactosamine, humic acid, shellac, pullulan, poly-gamma-glutamic acid, elastin, natural rubber, yeast glucans, synthetic polymers from natural fats and oils.”

Huang2 discloses all the required elements necessary to anticipate this claim.

(EX1003, §VI.A.6.) As discussed in §X.E., *supra.*, Huang2 discloses all the elements of claim 5. Huang2 also discloses the use of polycaprolactone as an accessory polymer, as called for by claim 6. Huang2 specifically uses

polycaprolactone (PCL) for its blended collagen-PCL fibers. (EX1005, 1792.)

Indeed, the ’223 patent specification identifies “polycaprolactone” as an exemplary “accessory polymer[.]” (EX1001, 12:7-26.) Accordingly, Huang2 anticipates this claim.

G. Claim 7: “The scaffold according to claim 1, wherein the scaffold comprises a bioactive factor.”

Huang2 discloses all the elements of this claim as arranged in the claim.

(EX1003, §VI.A.7.) As discussed in §X.A., *supra*., Huang2 discloses all the elements of claim 1. Further, Huang2 discloses a “bioactive factor.” As mentioned above, the ’223 patent specification describes a “bioactive factor” as “protein, carbohydrate, or mineral that has any effect on a cellular activity,” and lists “collagen” as an exemplary “bioactive factor.” (EX1001, 12:44-67.)

Similarly, Huang2 discloses a scaffold comprising *collagen*. (EX1005, 1792 (disclosing “type I collagen (Coll)” and fabrication of “[n]anofibrous matrices of PCL and Collagen”).)

Further, Huang2 explains how collagen affects cellular activity. As discussed above, Huang2 studies how the alignment of collagen containing fibers affects the proliferation of fibroblasts (normal human dermal fibroblasts) on bioengineered scaffolds: “In this study, the phenotypic expressions of normal human dermal fibroblasts (NHDFs) on collagen-containing nanofibrous matrices with either isotropic (i.e., fibers collected randomly with no alignment) or anisotropic (i.e., fibers collected with alignment) fiber organizations were studied by immunostaining, migration assay and molecular analyses.” (EX1005, 1791 (Abstract).) Huang2 explains that “[c]ollagen fibrils, a major ECM [extracellular matrix] component known for their mechanical contribution to skin integrity,

provide an interactive 3D microenvironment to skin cells and regulate their behaviors via cell-matrix interactions.” (EX1005, 1791.) This aligns with Huang2’s description that “[t]o better support and facilitate skin cells to form skin-like tissues, it is necessary for the temporary scaffolds not only to provide a surface for the cells to reside, but also to define a cell-friendly microenvironment that maximally recaptures the native extracellular matrix (ECM).” (*Id.*) As such, collagen is a “bioactive factor” within the meaning of claim 7. Accordingly, Huang2 plainly discloses all the elements of claim 7 and anticipates this claim.

H. Claim 8: “The scaffold according to claim 7, wherein the bioactive factor is selected from the group consisting of an osteogenic growth factor, collagen, glycosaminoglycans, osteonectin, bone sialo protein, an osteoinductive factor, a chondrogenic factor, a cytokine, a mitogenic factor, a chemotactic factor, a transforming growth factor (TGF), a fibroblast growth factor (FGF), an angiogenic factor, an insulin-like growth factor (IGF), a platelet-derived growth factor (PDGF), an epidermal growth factor (EGF), a vascular endothelial growth factor (VEGF), a nerve growth factor (NGF), a neurotrophin, a bone morphogenetic protein (BMP), osteogenin, osteopontin, osteocalcin, cementum attachment protein, erythropoietin, thrombopoietin, tumor necrosis factor (TNF), an interferon, a colony stimulating factor (CSF), stem cell derived factor-1 (SDF-1), and an interleukin.”

Huang2 discloses all the required elements necessary to anticipate this claim. (EX1003, §VI.A.8.) As discussed in §X.G., *supra.*, Huang2 discloses all the elements of claim 7. Further, Huang2 discloses the use of collagen as bioactive factor as called for by claim 7 of the ’223 patent, upon which claim 8 depends.

(See, §X.F., *supra*.) Claim 8 further defines the bioactive factor as including collagen and is thus also satisfied by the teaching of Huang2. Accordingly, Huang2 anticipates this claim.

I. Claim 9: “The scaffold according to claim 1, wherein the scaffold comprises an extracellular matrix component.”

Huang2 discloses all the elements of this claim as arranged in the claim. (EX1003, §VI.A.9.) As discussed in §X.A., *supra*., Huang2 discloses all the elements of claim 1. Additionally, Huang2 discloses the “extracellular matrix component” element of claim 9. (EX1003, §VI.A.9.) The ’223 describes “extracellular matrix components” that can be part of the “aligned fiber, electrospun fiber, and/or scaffold” as “includ[ing], but not limited to, collagen” (EX1001, 14:64-15:3 (emphasis added).) Huang2 similarly discloses the use of collagen in the scaffold, which the ’223 patent identifies as an extracellular matrix component. (EX1005, 1792 (disclosing fabrication of “[n]anofibrous matrices of PCL and Collagen”), 1794 (“Using the established electrospinning condition as described in Materials and Methods, PCL/Coll nanofibers [were] collected on a rotating mandrel or on a stationary surface had distinct spatial arrangements.”); EX1003, §VI.A.4.)) Huang2 discloses that “[c]ollagen fibrils, a major ECM component known for their mechanical contribution to skin integrity, provide an interactive 3D microenvironment to skin cells and regulate their behaviors via cell-matrix interactions.” (EX1005, 1791

(“To better mimic skin ECM, electrospun collagen fibers have been fabricated”).)

Accordingly, Huang2 discloses all the elements of claim 9 and anticipates this claim.

J. Claim 10: “The scaffold according to claim 9, wherein the extracellular matrix component is selected from the group consisting of collagen, glycosaminoglycans, osteocalcin, osteonectin, bone sialo protein, osteopontin, fibronectin, laminin, and mixtures thereof.”

Huang2 discloses all the required elements necessary to anticipate this claim.

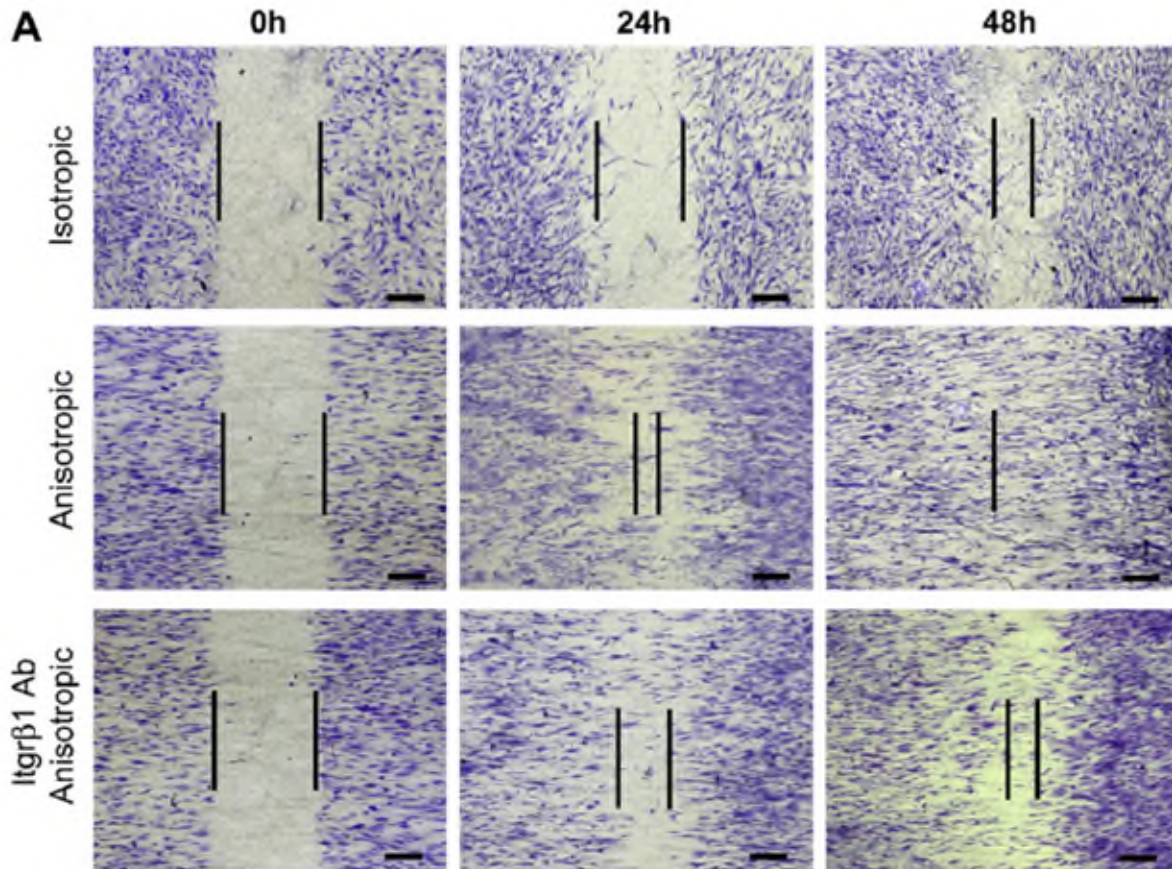
(EX1003, §VI.A.10.) As discussed in §X.I., *supra.*, Huang2 discloses all the elements of claim 9. Claim 10 further lists collagen as a component of the extracellular matrix, which is also disclosed by Huang2. For example, Huang2 discloses that “[c]ollagen fibrils, a major ECM component known for their mechanical contribution to skin integrity, provide an interactive 3D microenvironment to skin cells and regulate their behaviors via cell-matrix interactions.” (EX1005, 1791 (“To better mimic skin ECM, electrospun collagen fibers have been fabricated”).) Accordingly, Huang2 anticipates this claim.

K. Claim 11: “A method of cell culture comprising culturing cells on the scaffold according to claim 1 under conditions suitable for the cell culture”

Huang2 discloses all the elements of this claim arranged in the claim.

(EX1003, §VI.A.11.) As discussed in §X.A., *supra.*, Huang2 discloses all the elements of claim 1. Further, Huang2 discloses the cell culturing elements of this

claim. Huang2 teaches culturing fibroblasts under suitable conditions such that the cells grow. (EX1005, 1792.) Huang2 discloses that “fibroblasts were seeded on the nanofibrous matrices at a density of 5×10^3 cells/cm² 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, §VI.A.11; *see also* EX1005, 1799, Figs. 2-7.)



(EX1005, 1797 (Fig. 6A).)

Accordingly, Huang2 plainly discloses all the elements of claim 11.

L. Claim 12: “The method of claim 11, wherein the cells are selected from the group consisting of stem cells, adipose derived stem cells, dental pulp stem cells, fibroblasts, and dorsal root ganglia”

Huang2 discloses all the required elements necessary to anticipate this claim.

(EX1003, §VI.A.12.) As discussed in §X.K., *supra.*, Huang2 discloses all the elements of claim 11. Claim 12 further defined that cells cultured on the scaffold must be selected from the group that consist of fibroblasts. Huang2 specifically discloses culturing fibroblasts on nanofibrous electrospun matrices, noting the

“fibroblasts were seeded on the nanofibrous matrices at a density of 5×10^3 cells/cm² 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.) Accordingly, Huang2 anticipates this claim.

XI. GROUND 2: CLAIM 4 IS OBVIOUS OVER HUANG2 IN VIEW OF KUMBAR

To the extent not anticipated for the reasons set forth above (*see* §X.D., *supra*), Huang2 in view of Kumbar renders claim 4 obvious. (EX1003, § VI.B.) Claim 4 recites “[t]he scaffold according to claim 1, wherein the scaffold has an average porosity from about 60% to about 90%.” As mentioned above, Huang2 discloses a scaffold of electrospun fibers that include collagen that have aligned fibers with major peaks about 180° apart, as called for by claim 1 of the ’223 patent. (*See* §X.A., *supra*.)

Regarding the porosity element of claim 4, Huang2 explains that a goal of tissue-engineered skin grafts is to “define a cell-friendly microenvironment that maximally recaptures the native extracellular matrix (ECM). In this regard, electrospun nanofibrous matrices characterized by ultrafine continuous nanoscaled fibers, high surface-to-volume ratio, *high porosity* and variable pore-size distribution, have great potential to mimic the skin ECM in both morphology and composition [2, 3].” (EX1005, 1791) (emphasis added).) Huang2 cites Kumbar in

support of this disclosure. In particular, reference [3] is a citation to Kumbar.

(EX1005, 1799.)

Kumbar discloses methods of designing electrospun nanofiber matrix scaffolds “to provide cells with the necessary chemical cues and a more *in vivo* like environment” for use “in the regeneration of various soft tissues including skin[.]” (EX1006, 1 (Abstract).) Kumbar states that a “high porosity” is desirable as it more closely approximates the natural extra-cellular matrix or “ECM.” (*Id.*)

In its discussion of electrospun nanofiber skin grafts, Kumbar discloses that “collagen nanofibers play a dominant role in maintaining the biological and structural integrity of various tissues and organs, including bone, skin, tendon, blood vessels and cartilage.” (EX1006, 7.) In terms of porosity, Kumbar discloses that the collagen type I fibers had a porosity of 89%. (*Id.*) Kumbar also discusses that it can be useful to cross-link collagen type I nanofibers and that such cross-linked fibers were similar in strength to certain commercially available wound care products. (*Id.*) When these fibers were cross-linked, the porosity decreased to 71%. (*Id.*) Thus, with respect to fibers comprising collagen, Kumbar discloses porosity of samples at 89% or 71%, if crosslinked. (*Id.*, 7.) Both of these high porosity values are within the recited range of claim 4.

Accordingly, a POSA who desired to make aligned collagen blended fibers (as taught by Huang²) with “high porosity” (as also taught by Huang²) would have

been motivated to look at the reference cited by Huang2 in support of the “high porosity.” (EX1003, ¶169.) As Huang2 cites Kumbar for this point, there would have been strong motivation to combine Huang2 and Kumbar. Kumbar teaches the desirability of high porosity and further discloses ranges of porosity within the scope of claim 4, including collagen fiber scaffolds that have a porosity of 89% or 71%. (EX1006, 1, 6-7, 12; EX1003, ¶169.)

Further, both references are in the same field, involving using electrospun collagen-containing scaffolds for biomedical applications, such as in regenerative medicine (e.g., skin grafts). (*E.g.*, EX1005, 1791; EX1006, 1; EX1003, ¶170.) Both note that “electrospun nanofibrous matrices . . . characterized by . . . high porosity and variable pore-size distribution” show morphological similarities to natural skin ECM. (EX1005, 1791; EX1006, 1, 6, 12; EX1003, §VI.B.) And Huang2’s and Kumbar’s discussion of the benefits of mimicking the porosity of the native skin ECM would have further motivated a POSA to combine the teachings of Kumbar modify Huang2’s disclosed scaffolds to have porosity of 89% or 71%. (EX1003, § VI.B.; *see also* EX1006, 6-7.)

In addition, tailoring the porosity of electrospun fibers is well within the knowledge of a POSA, for example by using well-known methods including freeze-drying, salt leaching, and gas foaming. (EX1003, ¶171.) Such techniques have long been used on electrospun scaffolds, are well-understood, and allow a

POSA to achieve the predictable result of a desired porosity (e.g., about 60-90%) with a reasonable expectation of success. (EX1003, ¶171.) Accordingly, Huang² in view of Kumbar renders obvious all of the elements of claim 4.

XII. GROUND 3: CLAIMS 1-12 ARE ANTICIPATED BY LEE

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

Lee discloses all of the elements of this claim as arranged in the claim.

(EX1003, §VI.C.1.)

1. “A scaffold comprising:

Lee discloses this element of the claim. (EX1003, §VI.C.1.a.) The use of scaffolds made from electrospun fibers were well-known in the prior art, as shown during prosecution of the '223 patent, discussed above. (*See generally* Ex. 1002.) In this regard, Lee discusses extensively the use and preparation of scaffolds, demonstrating that scaffolds were well-known in the art. (EX1011, [0044]-0059].) Lee discloses that “fibers include natural polymers (e.g., collagen, elastin, etc.) and/or synthetic polymers (e.g., polycaprolactone (PCL)).” (EX1011, [0005].) Lee discloses that a scaffold “refers to an array of natural or synthetic matrix of molecules to which cells or fibers can attach.” (EX1011, [0044].) Lee notes that “a composite scaffolding system including PCL and collagen has been developed that possess excellent cell compatibility as well as maintains structural

integrity (EX1011 et al. (2008).)” (*Id.*, [0050]; *see also id.* [0055] (discussing additional disclosures of scaffolds in the prior art).) Lee further discloses that scaffolds can be biodegradable and made of biodegradable materials, which include PCL and collagen. (*Id.*, [0045]-[0046].) Lee notes that “a ‘biodegradable scaffold,’ ‘biodegradable mesh’ or ‘biodegradable matrix’ is a scaffold having materials capable of being degraded and/or absorbed in a subject’s body.” (*Id.*, [0045].) Accordingly, this claim element is plainly disclosed by Lee.

2. “one or more electrospun fibers comprising collagen.”

Lee discloses these elements of the claim. (EX1003, §VI.C.1.b.) As discussed above, Lee discloses that collagen and fibrin materials have been used for scaffolding systems. Lee noted that a concern was that “these biomaterials are limited by the tissue size that may be formed.” (*Id.*, [0052].) Thus, Lee disclosed that in some embodiments, “aligned electrospun mesh included a mixture or blend of PCL and/or collagen is combined with primary cultured human skeletal muscle cells for skeletal muscle cells for skeletal regeneration.” (*Id.*, [0052].) Lee discloses that “PCL-collagen composite scaffolds according to some embodiments have preferable mechanical properties . . .” (*Id.*) As discussed above, Lee describes “a mesh” as a scaffold. (See §XII.A.1, *supra.*) Lee also uses collagen type 1 in its preparation of the scaffold. (EX1011, [0062].) Further, Lee discloses that “biodegradable scaffolds are formed by the electrospinning technique.” (*Id.*,

[0054].) As described above, biodegradable materials used in Lee’s biodegradable scaffolds include collagen. (See §XII.A.1, *supra*.) As noted by Lee, “electrospinning is known in the art and has been used in the fabrication of tissue engineered scaffolds.” (EX1011, [0054].) Lee discloses that the electrospun fibers in some embodiments are nanofibers that “have an average diameter from 10, 100 or 200 nm to 400, 500, 750 or 1000 nanometers.” (*Id.*) According to Lee, “electrospun nanofiber meshes were fabricated using a blend of PCL and collagen with a ratio of 1:1 in weight.” (*Id.*, [0063].) Accordingly, these claim elements are plainly disclosed in Lee.

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

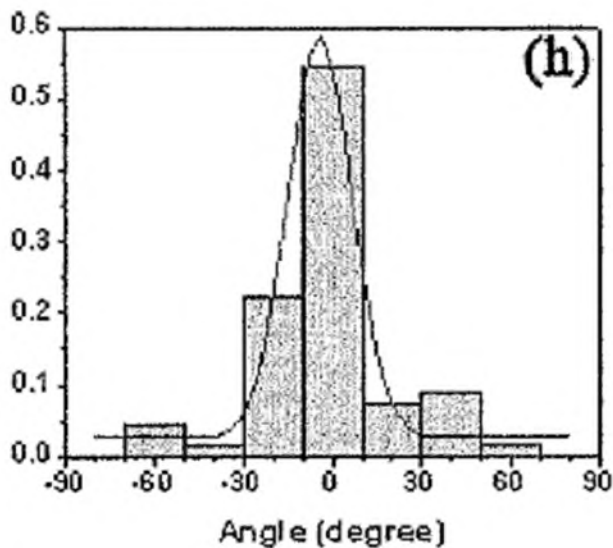
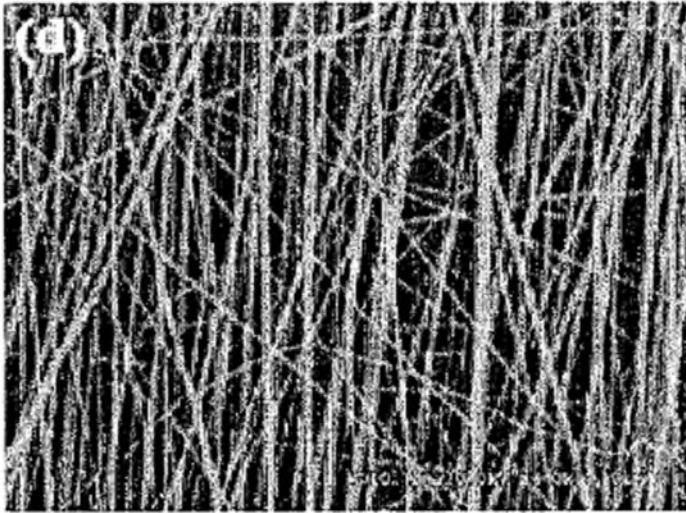
Lee discloses aligned PCL/collagen fibers that meet this element of the claim. (EX1003, §VI.C.1.c.) As noted above, an FFT analysis measures the degree of fiber alignment, and an FFT result showing fibers having adjacent major peaks with about 180° apart from each other would demonstrate that the fibers are aligned. 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. (EX1011, [0060]; *see* §IX.C., *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:

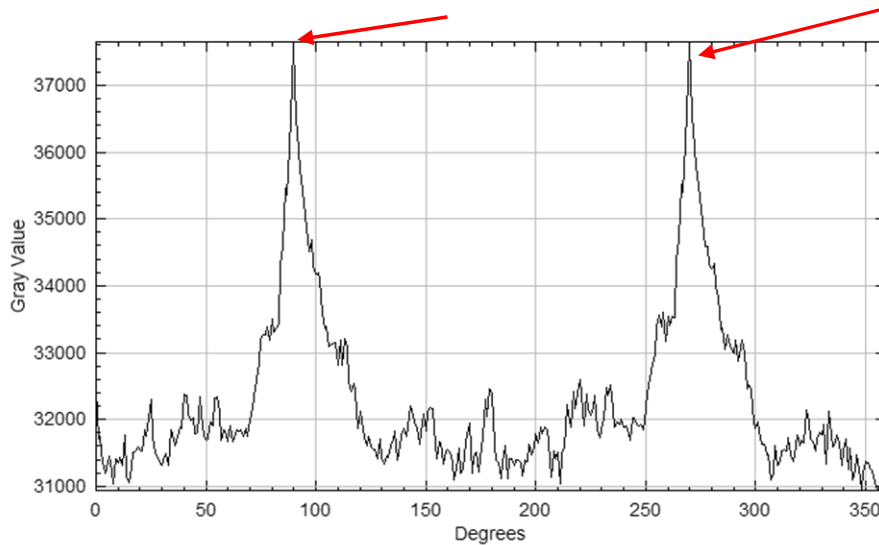


(EX1021, Figs. 1D, 1H.) The image analysis was done using Lee's provisional, U.S. Provisional Patent App. No. 61/025,350, which discloses the same data, but with a clearer image. Indeed, the scaffold in both Lee and its provisional are the same. (*E.g., compare* EX1011, [0062]-[0095] (materials and methods, results, discussion, conclusion) *with* EX1021, 14-24 (substantively identical); EX1003,

¶184.) The image analysis from Figures 1D and 1H show that Lee discloses highly aligned fibers. (*Id.*, [0012]; EX1003, §VI.C.1.c.)

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. (EX1011, [0066].) A POSA, however, would know that the degree of alignment could also be determined using ImageJ software to run an “FFT analysis.” An FFT analysis also measures the degree of orientation of fibers using a SEM image. This application of ImageJ software was well known at the time of filing of Lee. (EX1013, 4; EX1010, 607; EX1003, ¶186.) Further, it was well known at the time of filing of Lee that a FFT analysis could be performed to further confirm alignment. (*See* EX1010). 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 Figure 1D from Lee’s provisional, which has the same data as Figure 1D from Lee, and is clearer. (EX1003, ¶¶188-190.)



(EX1003, ¶¶188-190.) The resulting graph and analysis shows clear adjacent major peaks at around 90° and 270°. (EX1003, ¶¶188-190.) 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 (*Id.*) Indeed, Lee also performed tensile testing on the prepared electrospun fibers, which further confirms that Lee obtained aligned fibers. (EX1011, Figure 2, [0025], [0067], [0081], Claim 8; EX1003, ¶191.)

Accordingly, this element of claim 1, and indeed all the elements of claim 1, are disclosed by Lee, which anticipates claim 1.

B. Claim 2: “The scaffold according to claim 1, wherein the fibers comprise type I collagen in its native triple helical structure.”

Lee discloses all the elements of this claim as arranged in the claim.

(EX1003, §VI.C.2.) As discussed in §XII.A., *supra.*, Huang2 discloses all the elements of claim 1. Further, Lee specifically discloses electrospinning “oriented

nanofiber meshes” out of “PCL and type I collagen.” (EX1011, [0090], [0062]-[0063].)

Lee also discloses the “native triple helical structure” element of the claim. Lee disclosed that it obtained “[c]ollagen type I derived from calf skin,” which “was purchased from Elastin Products Company.” (EX1011, [0062].) Type I collagen was well-known and generally understood in the art to have a triple-helical form when it is in a monomer, as well as when it is in a polymer. (EX1017, 1, 9.) A POSA would have understood that, if the type 1 collagen purchased from a supplier were denatured and/or fragmented (i.e., not in a triple helix) it would be sold as “gelatin,” not “collagen.” (EX1003, ¶196.) In addition, Lee discloses that its scaffold was prepared by dissolving PCL and collagen in 1,1,1,3,3,3-hexafluoro-2-propanol, which is also known as “HFIP.” (EX1011, [0062]; EX1003, ¶117.) HFIP was known to stabilize collagen’s triple helix structure. (EX1015, 3782.) Indeed, the prior art demonstrated that collagen purchased from Elastin Products maintained its native triple helical structure when electrospun using HFIP as the solvent. (EX1015, 2778-79, 3782.) HFIP is also the same solvent used in the ’223 patent. (EX1001, 19:40-55 (example 1), 22:1-23 (example 2), 22:25-48 (example 3), 22:50-23:4 (example 4).) Accordingly, Lee plainly discloses all the elements of claim 2 and anticipates this claim.

C. Claim 3: “The scaffold according to claim 1, wherein the fiber has less than about 8 wt % residual calcium”

Lee discloses all the elements of this claim as arranged in the claim.

(EX1003, §VI.C.3.) As discussed in §XII.A., *supra.*, Huang² discloses all the elements of claim 1. Further, Lee discloses fabricating “electrospun nanofiber meshes using a blend of PCL and collagen with a ratio of 1:1 in weight.” (EX1011, [0063].) Lee lists “[c]ollagen type I derived from calf skin,” “poly(μ -caprolactone),” “1,1,1,3,3,3-hexafluoro-2-propanol (HFP),” and a “2.5% glutaraldehyde solution” crosslinker materials used to prepare its electrospun nanofiber scaffolds. (EX1011, [0062]-[0063].) Lee does not require or disclose using calcium or calcium-containing compounds in its electrospinning solution, electrospun fibers, or electrospun matrices, which would thus necessarily have less than about 8 wt % residual calcium. (EX1003, §VI.C.3.) Accordingly, Lee discloses all the elements of claim 3 and anticipates this claim.

D. Claim 4: “The scaffold according to claim 1, wherein the scaffold has an average porosity from about 60% to about 90%.”

Lee discloses all the elements of this claim as arranged in the claim.

(EX1003, §VI.C.4.) As discussed in §XII.A., *supra.*, Huang² discloses all the elements of claim 1. Further, Lee discloses the porosity element of this claim. Lee discloses “[e]lectrospun nanofiber scaffolds [that]...have a three-dimensional architecture, *high porosity* with an interconnected pore structure, and a high

surface-to-volume ratio, which provides a favorable environment for the cells to grow.” (EX1011, [0055] (emphasis added).) Lee explains that to achieve the desired “composition, structure, and mechanical properties,” its “biodegradable scaffold can be ‘shaped’ using methods such as...leaching,” “nucleation,” and “laser shaping.” (EX1011, [0055]-[0056].) Lee describes the salt leaching process as involving spreading “a solution containing two materials...into a shape that resembles the final form” and “dissolv[ing] away one of the components, resulting in pore formation (see U.S. Pat. No. 5,514,378 [Mikos]).” (*Id.*, [0056] (citing Mikos (EX1014)).) Lee incorporates Mikos by reference (*see* EX1011, [0021]), which describes the salt-leaching process in greater detail. In addition, as would have been understood by a POSA, Mikos states that “[h]igh porosity, greater than 80% volume, provides adequate space for cell seeding, growth, and extracellular matrix (ECM) production.” (EX1014, 13:15-17; EX1003, ¶204.) Accordingly, Lee, by itself and through its incorporation of Mikos, discloses high porosity values that are within the range of porosity recited by claim 4. As such, Lee discloses all the elements of claim 4 and anticipates this claim.

- E. Claim 5: “The scaffold according to claim 1, wherein the scaffold comprises collagen type I, bone matrix, adipose extracellular matrix, heart basement membrane extract, heart basement membrane extracellular matrix, placenta basement membrane extract, placenta basement membrane extracellular matrix, brain-derived extracellular matrix, polycaprolactone, an accessory polymer, or the mixture thereof.”**

Lee discloses all the required elements necessary to anticipate this claim.

(EX1003, §VI.C.5.) As discussed in §XII.A., *supra.*, Huang² discloses all the elements of claim 1. Further, Lee discloses a scaffold comprising at least collagen type I, polycaprolactone, and the mixture thereof. (EX1011, [0062] (listing “Collagen type I derived from calf skin” and “Poly(μ -caprolactone)” as components in Lee’s electrospinning solution), [0063] (“Electrospun nanofiber meshes were fabricated using a blend of PCL and collagen.”); *see also* Lee [0005]-[0007] (disclosing “a biodegradable scaffold comprising a plurality of fibers...[that] include natural polymers (e.g., collagen, elastin, etc.) and/or synthetic polymers (e.g., polycaprolactone (PCL)...”).).)

PCL is also an accessory polymer within the meaning of claim 5. (EX1003, §VI.C.5.) As discussed above, the ’223 describes an “accessory polymer” as “a polymer that may be added to the electrospun fibers and have any effect on [the fibers’] physical, chemical, and/or biological properties (e.g., tensile strength, hydrophilicity, biocompatibility). (EX1001, 12:7-26.) Lee explains that “PCL-collagen composite scaffolds...have preferable biomechanical properties, *e.g.*,

yield tensile strength, elasticity, and compliance. PCL is biodegradable synthetic polymer that supports high mechanical properties, especially, high elongation, but has lower biocompatibility compared to natural polymer such as collagen and elastin. Collagen has a good biocompatibility, but poor mechanical properties and processability. When PCL and collagen are combined together, the mesh can be improved biocompatibility, mechanical properties, and processability.” (EX1011, [0050], [0052].) Accordingly, Lee anticipates this claim.

F. Claim 6: “The scaffold according to claim 5, wherein the accessory polymer is selected from the group consisting of polycaprolactone, poly(glycolic acid), poly(lactic acid), polydioxanone, poly(lactide-co-glycolide) copolymers, polyesters polysaccharides, polyhydroxyalkanoates, starch, polylactic acid, cellulose, proteins, agar, silks, alginate, collagen / gelatin, carrageenan, elastin, pectin, resilin, konjac, adhesives, gums, polyamino acids, polysaccharides, soy, zein, wheat gluten, casein, chitin / chitosan, serum albumin, hyaluronic acid, lipids / surfactants, xanthan, acetoglycerides, waxes, surfactants, dextran, emulsan, gelatin, polyphenols, levan, lignin, curd, inulin, tannin, polygalactosamine, humic acid, shellac, pullulan, poly-gamma-glutamic acid, elastin, natural rubber, yeast glucans, synthetic polymers from natural fats and oils.”

Lee discloses all the required elements necessary to anticipate this claim. (EX1003, §VI.C.6.) As discussed in §XII.E., *supra.*, Huang2 discloses all the elements of claim 5. Indeed, as discussed above, Lee describes the use of PCL as an accessory polymer within the meaning of claim 5, upon which claim 6 depends. (See §XII.E., *supra.*) Accordingly, Lee anticipates this claim.

G. Claim 7: The scaffold according to claim 1, wherein the scaffold comprises a bioactive factor.”

Lee discloses all the elements of this claim as arranged in the claim.

(EX1003, §VI.C.7.) As discussed in §XII.A., *supra.*, Huang² discloses all the elements of claim 1. Further, Lee discloses the “bioactive factor” element of this claim. The ’223 describes a “bioactive factor” as “protein, carbohydrate, or mineral that has any effect on a cellular activity” and lists “collagen” as an exemplary “bioactive factor.” (EX1001, 12:44-67.)

Lee discloses that its electrospun scaffolds may be formed with natural polymers such as collagen for biocompatibility, cell adhesion, proliferation, and differentiation. (EX1011, [0095], [0005]-[0007], [0052]; *see also id.* [0062]-[0063] (“Electrospun nanofiber meshes were fabricated using a blend of PCL and collagen.”).) Lee further discloses that its “biodegradable scaffold can be treated with additives or drugs prior to implantation (before or after it is seeded with cells), e.g., to promote the formation of new tissue after implantation.” (EX1011, [0057].) Such additives include “growth factors, cytokines, extracellular matrix components, and/or other bioactive materials” and “will in general[] be selected according to the tissue or organ being reconstructed or augmented, to ensure that appropriate new tissue is formed in the engrafted organ or tissue.” (*Id.*)

As described above, collagen is a bioactive factor. (EX1003, ¶¶217-218; *see also* Lee [0052] (“Collagen has a good biocompatibility.”).) Elastin and fibrin, as

well as growth factors, cytokines, extracellular matrix components, and/or other bioactive materials are also bioactive factors. (EX1003, ¶218.) According to Lee, such additives “can be added to the biodegradable scaffold to promote graft healing and the formation of new tissue.” (EX1011, [0057].) Thus, Lee discloses all the elements of claim 7 and anticipates this claim.

H. Claim 8: “The scaffold according to claim 7, wherein the bioactive factor is selected from the group consisting of an osteogenic growth factor, collagen, glycosaminoglycans, osteonectin, bone sialo protein, an osteoinductive factor, a chondrogenic factor, a cytokine, a mitogenic factor, a chemotactic factor, a transforming growth factor (TGF), a fibroblast growth factor (FGF), an angiogenic factor, an insulin-like growth factor (IGF), a platelet-derived growth factor (PDGF), an epidermal growth factor (EGF), a vascular endothelial growth factor (VEGF), a nerve growth factor (NGF), a neurotrophin, a bone morphogenetic protein (BMP), osteogenin, osteopontin, osteocalcin, cementum attachment protein, erythropoietin, thrombopoietin, tumor necrosis factor (TNF), an interferon, a colony stimulating factor (CSF), stem cell derived factor-1 (SDF-1), and an interleukin.”

Lee discloses all the required elements necessary to anticipate this claim. (EX1003, §VI.C.8.) As discussed in §XII.G., *supra.*, Huang² discloses all the elements of claim 7. Further, Lee, at the very least, discloses the use of collagen as a bioactive factor as called for by claim 7 of the ’223 patent, upon which claim 8 depends. (See §XII.G., *supra.*) Accordingly, Lee anticipates this claim.

I. Claim 9: “The scaffold according to claim 1, wherein the scaffold comprises an extracellular matrix component.”

Lee discloses all the elements of this claim as arranged in the claim.

(EX1003, §VI.C.9.) As discussed in §XII.A., *supra.*, Huang² discloses all the elements of claim 1. Further, Lee discloses the “extracellular matrix component” element of this claim. The ’223 patent describes “extracellular matrix components” that can be part of the “aligned fiber, electrospun fiber, and/or scaffold” as “includ[ing], but not limited to, *collagen*, glycosaminoglycans, osteocalcin, osteonectin, bone sialo protein, osteopontin, fibronectin, laminin, and mixtures thereof.” (EX1001, 14:64-15:3 (emphasis added).) Lee states that its “[s]caffolds may include *extracellular matrix components*, such as elastin, elastin-like or elastin-mimetic peptides, fibrin, proteoglycans, commercially available matrix or matrix-substitutes..., collagen of any type, synthetic fibers or fibrils, or bioactive hydrogels” or be made of “fibers...include[ing] extracellular matrix molecules or components, such as elastin, elastic strands or peptides, fibrin, collagen, proteoglycans, hyaluronan or hyaluronan oligomers, synthetic fibers or fibrils, or bioactive hydrogels, microparticles, beads, liposomes, or vesicles.” (EX1011, [0044].) And Lee explains that “extracellular matrix components . . . can be added to the biodegradable scaffold to promote graft healing and the formation of new tissue.” (*Id.*, [0057].) Accordingly, Lee discloses all the elements of claim 9 and anticipates this claim.

J. Claim 10: “The scaffold according to claim 9, wherein the extracellular matrix component is selected from the group consisting of collagen, glycosaminoglycans, osteocalcin, osteonectin, bone sialo protein, osteopontin, fibronectin, laminin, and mixtures thereof.”

Lee discloses all the required elements necessary to anticipate this claim.

(EX1003, §VI.C.10.) As discussed in §XII.I., *supra.*, Huang2 discloses all the elements of claim 9. Claim 10 further lists collagen as a component of the extracellular matrix, which is also disclosed by Lee. For example, as discussed above, Lee discloses “[s]caffolds [that] may include extracellular matrix molecules or components, such as . . . proteoglycan . . . [or] collagen of any type,” and mixtures thereof. (EX1011, [0044].) Thus, not only does Lee disclose collagen, but by disclosing proteoglycans, it also discloses glycosaminoglycans, which are recited by claim 10. (*Id.*, [0044]; EX1003, ¶231.) Accordingly, Lee anticipates this claim.

K. Claim 11: “A method of cell culture comprising culturing cells on the scaffold according to claim 1 under conditions suitable for cell culture”

Lee discloses all the elements of this claim as arranged in the claim.

(EX1003, §VI.C.11.) As discussed in §XII.A., *supra.*, Huang2 discloses all the elements of claim 1. Further, Lee discloses culturing cells on the scaffold under conditions suitable for the cell culture. Lee specifically discloses “seeding...skeletal muscle cells on a scaffold comprising oriented [collagen-

containing] fibers” and “growing said cells on said scaffold in a growth medium,” which “is a high serum medium that promotes the expansion of cells with or without minimal differentiation.” (EX1011, Claims 16, 18, 20, [0037], [0007]; *see also* Lee [0058]-[0059] (“Seeding of cells onto the biodegradable scaffold may be performed according to standard methods” and describing standard seeding methods.)) Lee notes that “the muscle cells readily adhered and proliferated for up to 7 days in culture, indicating that the nanofiber meshes were conducive to cell adhesion and proliferation.” (*Id.*, [0083]; *see also id.*, Fig. 4, [0064] (“For cell culture studies, the electrospun PCL/collagen nanofiber meshes were placed into 6-well plates, gas sterilized by ethylene oxide...at 30° C. for 36 hr, and incubated at 37° C. for 30 min in culture medium prior to cell seeding.”).) Accordingly, Lee discloses all the elements of claim 11 and anticipates this claim.

L. Claim 12: “The method of claim 11, wherein the cells are selected from the group consisting of stem cells, adipose derived stem cells, dental pulp stem cells, fibroblasts, and dorsal root ganglia”

Lee discloses all the required elements necessary to anticipate this claim. (EX1003, §VI.C.12.) As discussed in §XII.K., *supra.*, Huang² discloses all the elements of claim 11. Indeed, as set forth above, Lee discloses methods of culturing cells such that they will grow on the scaffold of claim 1, as required by claim 11, upon which claim 12 depends. (*See* §XII.K., *supra.*) Lee further discloses the particular cell types required by claim 12. (EX1003, ¶239.) Claim 12

requires that the cells that are cultured on the scaffold include “stem cells.” Lee plainly discloses this element. Lee discloses that “[s]keletal muscle cells may be provided by isolating cells from skeletal muscle tissue harvested from the skeletal muscle of an organism, differentiating *stem* or progenitor cells (e.g., embryonic or amniotic fluid stem cells), etc.” (EX1011, [0040] (emphasis added).) Lee also states that “[s]keleton muscle cells include . . . myoblasts.” (*Id.*) Lee specifically defines “myoblasts” as “a type of *muscle stem cell*, and are normally closely associated with myofibers during the course of their life cycle” (*Id.*, [0030] (emphasis added).) Accordingly, Lee discloses culturing stem cells on the scaffold made with aligned collagen nanofibers and thus anticipates this claim.

XIII. GROUND 4: CLAIMS 1-12 ARE OBVIOUS IN VIEW OF LEE ALONE

As set forth in detail above, Lee discloses to a POSA each of the required elements of claims 1-12 of the '223 patent necessary to anticipate each such claim. In the alternative, if the claims are found not to be anticipated by Lee, then they are obvious in view of Lee alone under 35 U.S.C. §103. In particular, for the element of claim 1 of the '223 patent, “wherein a fast Fourier transform (FFT) analysis result of the fibers have adjacent major peaks with about 180° apart from each other,” there would have been motivation and a reasonable expectation of success for a POSA to run an FFT on the aligned fibers fabricated in Lee.

As noted above, in Lee, the investigators investigated the impact of alignment and the orientation of electrospun PCL/collagen nanofibers on the performance and properties of electrospun scaffolds. (EX1011, [0060], [0061], [0080]; *see* §IX.C., *supra*.) “[F]iber morphologies of the electrospun PCL/collagen nanofiber meshes were examined by scanning electron microscopy (SEM; Model S-2260N, Hitachi Co., Ltd, Japan).” (*Id.*, [0065].) Lee concluded that the fibers obtained were aligned through both mechanical testing and also by calculating the angles of alignment for the fibers. (*Id.*, [0065], [0067], [0081]; Fig. 1H; EX1003, ¶242.)

As discussed above (*see* §XII.A.3., *supra*), to determine fiber orientation in Lee, Fig 1H, Lee’s “SEM images were analyzed with UTHSCSA ImageTool 3.0 (Freeware provided by the University of Texas Heal Sciences Center, San Antonio, Tex., USA).” (*Id.*, [0066].) It was, however, well within the ordinary knowledge of a POSA at the applicable time that “FFT analysis” and ImageJ software could be run on Lee’s SEM images to confirm the degree of alignment. (EX1003, ¶243.) Ayres 2008 (EX1010) had been published for years as of the alleged filing date for the ’223 patent and was an established tool that was well-within the routine skill of a POSA at the time. (EX1003, ¶243.) Thus, a POSA would have been motivated to confirm the alignment with a well-known tool. (EX1003, ¶243.) And a POSA would have more than a reasonable expectation of success of successfully running

an FFT on Lee's SEM images, as demonstrated by Dr. Simpson above. (See §XII.A.3., *supra*.) Dr. Simpson's FFT analysis and graphing shows clear adjacent major peaks at around 90° and 270°, which are 180° apart from each other, and thus showing that Lee's collagen/PCL fibers fall within the scope of claim 1. (EX1003, ¶¶188-190.) Accordingly, even if this element of the claim is found not to be anticipated, it would have plainly been obvious based on Lee alone, when viewed from the perspective of a POSA. Accordingly, this element of claim 1, and indeed all the other elements of claims 1-12, which are plainly disclosed by Lee, would have at the very least been obvious in view of Lee. (See § XII.A-L, *supra*; EX1003, ¶¶241-45.)

XIV. 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: Embody, Inc. plans 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 Huang2, Lee, nor

Kumbar were considered during prosecution of the '223 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 Adv. 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.

XV. CONCLUSION

For the reasons above, Petitioners respectfully request institution of *inter partes* review and cancellation of claims 1-12 of the '223 patent as anticipated and/or obvious in view of the prior art.

XVI. 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

Date: 12/4/24

/David Feigenbaum/

CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that the foregoing **Petition for *Inter Partes* Review** contains 13404 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. 10,137,223 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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