

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

LIFENET HEALTH,
Patent Owner.

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

**DECLARATION OF DR. ANTONIOS G. MIKOS, PH.D.
IN SUPPORT OF PATENT OWNER'S RESPONSE**

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I, Antonios G. Mikos, Ph.D., declare as follows:

I. INTRODUCTION

A. Engagement

1. My name is Antonios G. Mikos, and I have been retained by McGuireWoods LLP, counsel for Patent Owner LifeNet Health (“LifeNet” or “Patent Owner”) as a technical expert in the above-captioned matter.

2. I am a contracting expert with IMS Legal Strategies (“IMS”). IMS is being compensated at a rate of \$1050 per hour for my expert consultation and travel, and \$1250 per hour for my deposition and any trial testimony, for my services in this matter. No part of my compensation is dependent on my opinions or on the outcome of this proceeding. I have no financial interest in any of the parties.

3. I have been asked by counsel for Patent Owner to offer an expert opinion on the four asserted grounds of invalidity presented by Embody, Inc. and Zimmer Biomet Holdings Inc. (“Embody” or “Petitioner”) against claims 1-8 (the “Challenged Claims”) of U.S. Patent No. 11,318,227 (the “’227 patent”) (Ex. 1001).

B. Qualifications

4. I am currently the Louis Calder Professor of Bioengineering and Chemical and Biomolecular Engineering, Departments of Bioengineering and Chemical and Biomolecular Engineering, at Rice University in Houston, Texas. I have taught both undergraduate and graduate courses in biomaterials, tissue

engineering, biosystems transport and reaction processes, and chemical engineering.

5. I am also President, Biomedical and Informatics Consultants, Inc., a position I have held since 2002.

6. My expertise is in the field of biomaterials and more particularly in creating and evaluating novel orthopedic, cardiovascular, and neurologic biomaterials for use as, among other things, scaffolds for tissue engineering, as carriers for controlled drug delivery, and as non-viral vectors for gene therapy. In this capacity, I have studied and worked extensively with various mechanisms for creating scaffolds for tissue engineering, including electrospinning, and with various mechanisms for evaluating the characteristics of such scaffolds, including fast Fourier transform.

7. I received a Dipl. Eng. from the Aristotle University of Thessaloniki, Greece in 1983, an M.S. in Chemical Engineering from Purdue University in 1985, and a Ph.D. in Chemical Engineering from Purdue University in 1988.

8. After completing my graduate studies, I was a postdoctoral researcher in the Department of Chemical Engineering at the Massachusetts Institute of Technology and the Department of Surgery at The Children's Hospital of Boston, Harvard Medical School.

9. I joined the faculty at Rice University in 1992 as an assistant professor. Since joining Rice University, I have served as the Director of the Center for

Excellence in Tissue Engineering, the Director of the John W. Cox Laboratory for Biomedical Engineering, and the John W. Cox Professor of Bioengineering and Chemical and Biomolecular Engineering.

10. In addition to my professorship, I am a founding editor and the Editor-in-Chief of the journals *Tissue Engineering Part A*, *Tissue Engineering Part B: Reviews*, and *Tissue Engineering Part C: Methods*. I currently serve on the editorial boards of numerous journals in the area of biomaterials, including *Advanced Drug Delivery Reviews*, *Cell Transplantation*, *Journal of Biomaterials Science - Polymer Edition*, *Journal of Biomedical Materials Research*, *Journal of Controlled Release*, *Regenerative Biomaterials*, *Tissue Engineering Intelligence Unit*, and *Tissue Engineering Series*. I formerly served on the editorial boards of several additional journals, including *Biomaterials* and *Annual Review of Biomedical Engineering*.

11. I was awarded the *Founders Award* and the *Clemson Award for Contributions to the Literature* by the Society For Biomaterials. Additionally, among other recognitions, I have been awarded the *Robert A. Pritzker Distinguished Lectureship Award* of the Biomedical Engineering Society; the *Alpha Chi Sigma Award for Chemical Engineering Research* and the *Food, Pharmaceutical and Bioengineering Award in Chemical Engineering* by the American Institute of Chemical Engineers; the *Distinguished Scientist Award-Isaac Schour Memorial Award* by the International Association for Dental Research; and the *Meriam/Wiley*

Distinguished Author Award by the American Society for Engineering Education.

12. I have also been elected to the National Academy of Engineering, the National Academy of Medicine, the American Academy of Arts and Sciences, the National Academy of Inventors, and the Texas Academy of Medicine, Engineering, Science and Technology. I am a Founding Fellow of the Tissue Engineering and Regenerative Medicine International Society, a Fellow of the American Institute for Medical and Biological Engineering, a Fellow of the International Union of Societies for Biomaterials Science and Engineering, a Fellow of the Biomedical Engineering Society, a Fellow of the Controlled Release Society, and a Fellow of the American Association for the Advancement of Science.

13. I am also a member of numerous professional societies. I have served as the President of the Society for Biomaterials. I have also served as the Continental Chair of the Tissue Engineering and Regenerative Medicine International Society for Americas. I am also a member of the American Institute for Medical and Biological Engineering, the Biomedical Engineering Society, and the Materials Research Society.

14. I am an author or coauthor of more than 710 scientific publications and 33 patents. I am an editor of 15 books and the author of one textbook (Biomaterials: The Intersection of Biology and Materials Science, Pearson, 1st ed., 2008 and 2nd ed., 2023). I have been cited over 110,000 times.

15. A complete list of my publications and a description of my other credentials and accomplishments are provided in my *curriculum vitae*, which is attached as Ex. 2016.

C. Materials Considered

16. My opinions are based on my years of education, research and experience in the field of biomaterials, as well as my investigation and study of relevant materials. In forming my opinions, I have reviewed the Petition filed by Petitioner (Paper 2 (“Pet.”)), the materials cited in the Petition, the Patent Owner Preliminary Response (Paper 9), and the additional materials cited in Appendix A.

17. I may rely upon these materials and/or additional materials to rebut any further arguments raised by Petitioner. Further, I may also consider additional documents and information in forming any necessary opinions, including documents that I may not yet have reviewed and documents that have not yet been provided to me.

18. My analysis of the materials relating to this proceeding is ongoing and I will continue to review any new material as it is provided. This declaration represents those opinions I have formed to date. I reserve the right to revise, supplement, and/or amend my opinions based on new information and on my continuing analysis of the materials referred to herein and listed in Appendix A.

II. LEGAL STANDARDS

19. I am not a lawyer and have no training in the field of law. Therefore, I offer no opinions on the law. However, certain legal principles that relate to my opinions have been explained to me.

20. I understand that for a patent claim to be valid and patentable, it must be, among other things, new and not obvious considering what came before it. That which was known or came before the invention claimed in a patent is generally referred to as “prior art.”

21. I understand that the claims must be construed in accordance with the ordinary and customary meaning of the claim language, as understood by one of ordinary skill in the art and in light of the prosecution history of the patent. The claims, after being construed in this manner, are then compared to the prior art.

22. I understand that there are two ways in which prior art may render a patent claim unpatentable. First, the prior art can be shown to anticipate the claim. Second, the prior art can be shown to have rendered the claim obvious to a person of ordinary skill in the art.

23. I further understand that information that constitutes prior art generally must have been publicly disclosed before the earliest date of the claimed invention.

A. *Inter Partes* Reviews

24. I understand that, in this *inter partes* review proceeding, the burden is

on Petitioner to prove unpatentability by a preponderance of the evidence. I understand that “a preponderance of the evidence” is generally understood to require evidence sufficient to show that a given fact is more likely true than not true.

25. I understand that in this proceeding, the information upon which patentability may be evaluated is limited to prior art patents and printed publications. My analysis below compares the claims of the '227 patent to the patents and printed publications that are identified in the Petition.

B. Anticipation

26. I understand that the following standards govern the determination of whether a patent claim is anticipated by the prior art. I have applied these standards in my analysis.

27. I understand that, for a patent claim to be anticipated by the prior art, each and every element of the claim must be found, either expressly or inherently, in a single prior art reference.

28. I understand that claim elements that are not expressly found in a prior art reference may be inherently disclosed if the prior art necessarily includes that claim element. I also understand that the mere possibility or probability that the prior art may include a claim element is not sufficient to establish inherency. Instead, the limitation must be necessarily present in all circumstances.

C. Obviousness

29. I understand that the following standards govern the determination of whether a patent claim would have been obvious in light of the prior art. I have applied these standards in my analysis.

30. I understand that the obviousness standard is defined in the patent statute, 35 U.S.C. § 103(a), as follows:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

31. I understand that a claim in a patent is obvious when the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art (“POSITA”) to which the subject matter pertains.

32. I understand that an obviousness analysis considers the scope and content of the prior art, the differences between the claimed subject matter and the prior art, the knowledge of a POSITA at the time of the invention, and any objective indicia of non-obviousness. I also understand that the obviousness inquiry should not be performed with the benefit of hindsight but should be considered through the eyes of a POSITA at the time of the claimed invention.

33. I understand that the U.S. Supreme Court has recognized several rationales for combining prior art references or modifying a reference to show obviousness of the claimed subject matter. Some of these rationales include: combining prior art elements according to known methods to yield predictable results; simple substitution of one known element for another to obtain predictable results; a predictable use of prior art elements according to their established functions; applying a known technique to a known device (method or product) ready for improvement to yield predictable results; choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; and some teaching, suggestion, or motivation in the prior art that would have led a POSITA to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

34. I understand that when prior art is combined or modified in some manner to achieve the claim limitations, the proper inquiry in determining whether that would have been obvious is not whether a POSITA “could have” combined or modified the prior art in some manner, but whether they “would have” had some reason to do so.

35. I understand that where there is a reason to modify or combine prior art, the patent claim may be obvious if there is also a “reasonable expectation of success,” which refers whether a POSITA would have found a likelihood of success

in combining or modifying the prior art to meet the limitations of the claim. I understand that a reasonable expectation of success may be shown in different ways including through the prior art teachings or as part of the obviousness analysis. I also understand that absolute predictability of success is not required, but that a reasonable expectation of success is.

36. To evaluate the differences between prior art and the claimed subject matter, I understand that 35 U.S.C. § 103 requires the claimed invention to be considered as a whole. This requires showing that a POSITA at the time of the invention, with no knowledge of the claimed invention, would have selected the elements from the prior art and modified or combined them in the claimed manner.

37. Lastly, I am advised that an obviousness analysis must consider whether there are additional factors that would indicate that the invention was not obvious. Such factors include whether the invention was commercially successful, whether there was a long-felt need for the invention, whether others tried and failed to make the invention, whether others copied the invention, and any other facts that would suggest that someone with ordinary skill in the art would not have found the invention to have been obvious.

D. Level of Ordinary Skill in the Art

38. The Petition contends that a POSITA of the '227 patent “would be a Ph.D. student with a minimum of two years of experience in their faculty advisor’s

laboratory. At the relevant time, a [POSITA] would have understood the following technologies and techniques: electrospinning fibers, including for tissue engineering, tissue engineering techniques, and using/performing FFT analysis.” Pet. 20-21.

39. I generally agree with Petitioner’s identification of the level of ordinary skill in the art, however, I would further specify that “the Ph.D. student with a minimum of two years of experience in their faculty advisor’s laboratory,” identified by Petitioner, would have earned their Ph.D. in bioengineering, chemical engineering, mechanical engineering, or a related engineering discipline.

40. As of the earliest effective date of the ’227 patent, *see infra* § III.A, my experience exceeded both identified levels of ordinary skill in the art. I have applied the perspective of a POSITA when evaluating the validity of the ’227 patent.

III. THE ’227 PATENT

A. Effective Filing Date

41. In this proceeding, I apply March 14, 2013, the filing date of the provisional application to U.S. Patent No. 10,137,223, which is the parent to the application that issued as the ’227 patent, as the earliest effective filing date for this patent.

B. Disclosure

42. The '227 patent describes a “scaffold comprising an aligned fiber.” Ex. 1001, Abstract. The '227 patent describes using this scaffold to facilitate growth of various tissues to form biocompatible engineered tissues for use to repair damaged or diseased tissue. *Id.* at 11:28–57, 16:18–20. The '227 patent also described methods of treating a tissue by administering the disclosed scaffold to a tissue defect (e.g. osseous defects, defects in cartilage, ligament, tendon ...).” *Id.* at 18:54–62, 16:53–17:5.

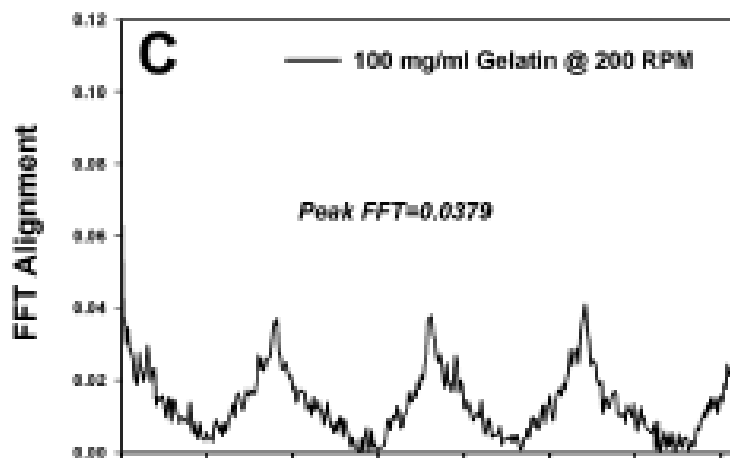
43. The '227 patent's scaffolds may be formed by electrospinning. *Id.* at 13:23–25. Electrospinning was known to generate very small diameter fibers, which the '227 patent describes as being “as small as one nanometer.” *Id.* at 2:42–44. The '227 patent states that its electrospun scaffolds may comprise collagen fibers. *Id.* at 13:50–14:2. The '227 patent also explains that the fibers may be crosslinked. *Id.* at 12:49–52.

44. The '227 patent discloses embodiments where electrospun fibers are aligned in one direction. *Id.* at Abstract.

45. To measure alignment of the scaffold's fibers, the '227 patent employs a fast Fourier transform (“FFT”) analysis, which is described in a 2008 publication authored by Dr. Simpson, Petitioner's expert witness, and which the patent incorporates by reference. *Id.* at 13:38–49.

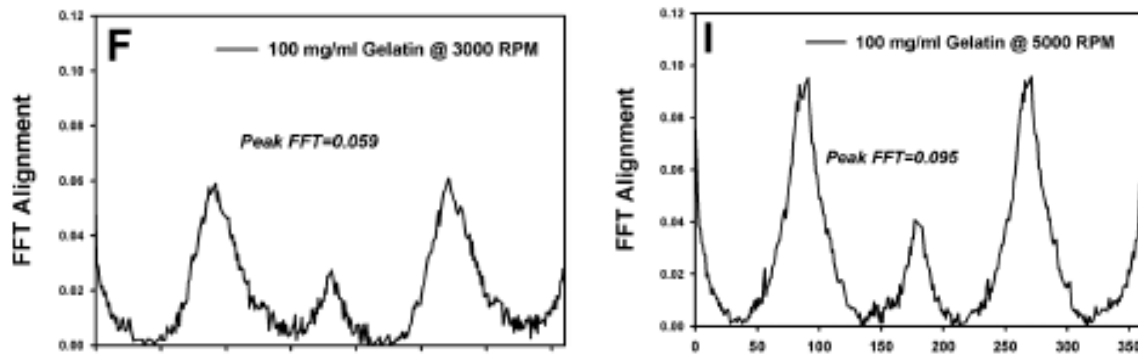
46. The incorporated 2008 paper describes using FFT analysis “to measure fiber alignment in electrospun materials.” Ex. 1010, Abstract. “The 2D FFT function converts spatial information in an optical data image into a mathematically defined frequency domain,” which “maps the rate at which pixel intensities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

47. The 2008 paper explains that a FFT analysis result for “a random matrix will exhibit 4 peaks that occur every 90°. Peaks of nearly uniform height are a hallmark of a scaffold composed of random elements,” as shown below in Figure 1C from the 2008 paper. *Id.* at 609.



Ex. 1010, 608 at Fig. 1C.

48. By contrast, FFT “plots generated from sample scaffolds containing aligned elements exhibit asymmetrical peaks, two larger peaks at 90 and 270° and two smaller peaks at 0 and 360° (Fig. 1F and I),” as shown below. *Id.* at 610.



Ex. 1010, 608 at Figs. 1F, 1I.

49. Dr. Simpson’s 2008 paper explains that the plot of a FFT analysis result highlights features of the distribution of fibers. For example, he states that “the height and overall shape of the most prominent peaks present in the alignment plot” conveys “[t]he degree of alignment present in the original data image” where “[a] high and narrow peak indicates a more uniform degree of fiber alignment, [but] a broad peak, or a shoulder on the peak indicates that more than one axis of alignment may be present.” *Id.* He also states that “the principal axis of fiber alignment is determined by the position of the alignment peaks.” *Id.* at 610.

50. The FFT analysis result of the scaffold claimed in the ’227 patent shows “adjacent major peaks with about 180° apart from each other,” where “major peaks” “refer to peaks higher than the average of the peaks in the result,” as shown in Figure 8A of the ’227 patent, shown below. Ex. 1001, 13:25–29.

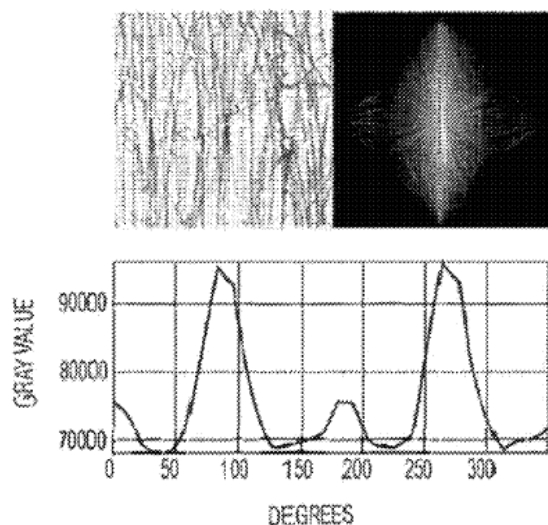


FIG. 8A

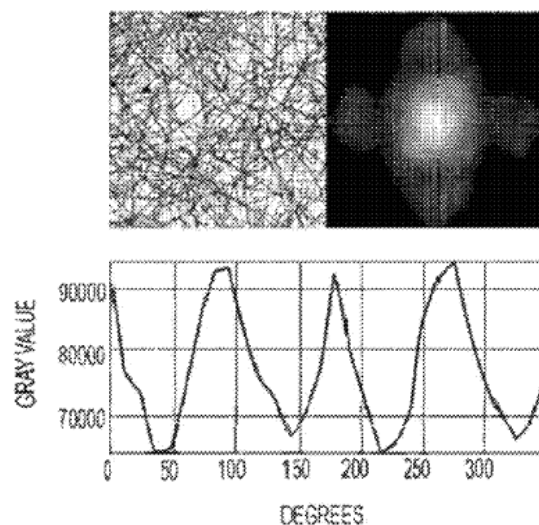


FIG. 8B

Id. at 13:25–29, Figs. 8A–8B.

51. The '227 patent's Figure 8A shows a FFT analysis result of aligned fibers, and Figure 8B as shown a control sample, e.g., with random fibers. *Id.* at 13:46-49. As shown above, the FFT analysis result in the '227 patent shows “adjacent major peaks with about 180° apart from each other” (Figure 8A), while the FFT analysis result for non-aligned fibers does not (Figure 8B). *Id.* at 13:46–49.

52. The '227 patent also describes that specific cells may be grown on the scaffold to repair specific tissues. *Id.* at 10:56–57, 16:26–27. For example, the '227 patent explains that “differentiation of stem cells into osteoblasts, chondrocytes, ligament or tendon” is promoted by “culturing the cells on the scaffold or aligned fiber described herein in conditions suitable for the cell differentiation.” *Id.* at 1:31–35, 16:54–18:17.

C. Challenged Claims

53. Claims 1 and 7 are the only challenged independent claim, and recite:

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

Claim 7. A method of cell culture comprising placing cells on a scaffold comprising aligned fibers, wherein a result of a FFT analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other, and growing the cells in conditions suitable for the cell culture.

Ex. 1001, 23:29-37, 24:5-11.

D. Claim Construction

54. I understand that the claims are to be interpreted based on the ordinary and customary meaning of the claim language, as understood by a POSITA in light of the patent and its prosecution history. I understand that the ordinary and customary meaning of a term is the meaning that the term would have had to a POSITA at the time of the invention.

55. Independent claim 1 recites: “a result of a fast Fourier transform (FFT) analysis of the fibers demonstrates that the fibers have major adjacent peaks that are about 180° apart from each other.” Ex. 1001, 23:33–35. Independent claim 7 includes similar language. A POSITA would understand the definition and meaning

of the term “major peaks” is provided in the ’227 patent itself: “[t]he ‘major peaks’ herein refer to peaks higher than the average of the peaks in the result.” *Id.* at 13:28–29.

56. This definition is consistent with the peaks shown in Figure 8A, reproduced below.

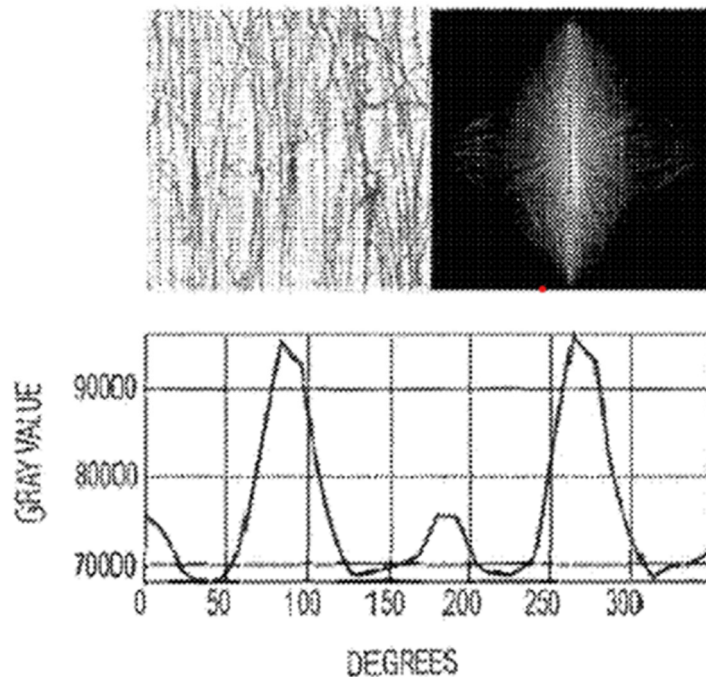


FIG. 8A

57. Based on the description in the ’227 patent, a POSITA would have understood the peaks at 90° and 270° of Figure 8A to be “major peaks” because they are higher than the average of the four peaks depicted in the result. More specifically, Figure 8A depicts peaks at 0°, 90°, 180°, and 270°, but the peaks at 0° and 180° are much shorter than those at 90° and 270°. The peaks at 90° and 270°

have heights of approximately 95,000 units, while the peaks at 0° and 180° have heights of approximately 75,000. Accordingly, the average height of the four peaks depicted in the result is 85,000 and the peaks at 90° and 270° are higher than that average.

58. This is consistent with how a POSITA would have understood the claim language. A POSITA would understand that the most prominent, or “major,” peaks in a FFT result have heights higher than the heights of the other peaks present in the FFT. The FFT process plots the high frequency signals in the image, which reflect fiber alignment, as prominent or “major” peaks that depict the extent of fiber alignment. *See, e.g.*, Ex. 1010, 610 (“The degree of alignment present in the original data image is reflected by the height and overall shape of the most prominent peaks present in the alignment plot. A high and narrow peak indicates a more uniform degree of fiber alignment.”); Ex. 1001, Figs. 8A-B.

59. A POSITA would have understood that a FFT plot may also include other peaks, for example, smaller or “minor” peaks. *See, e.g.* Ex. 1001, Fig. 8A. Smaller or minor peaks reflect fibers that present additional orientations. Ex. 1010, 610 (explaining that a “shoulder on the peak indicates that more than one axis of alignment may be present”). A POSITA would have understood that minor peaks depicted in an FFT result will lower the average peak height value, which may lead to the identification of additional “major” peaks.

60. In light of the '227 patent's definition and the understanding in the relevant art, a POSITA would interpret the claim language as "adjacent major peaks with about 180° apart from each other where each major peak has a height higher than the average of the peaks in the result."

IV. ANALYSIS OF ASSERTED GROUNDS

A. Identification of Asserted Grounds

61. I understand that Petitioner identifies the following challenges (Pet. 4):

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

B. Ground 1: Alleged Obviousness over Huang2 and Kuo

62. In my opinion, Huang2 and Kuo do not render obvious claims 1-6.

1. Claim 1

a) **"A method of treating a tissue defect in a subject comprising implanting at the tissue defect a scaffold comprising crosslinked fibers comprising collagen ..."**

63. Huang2 does not disclose "crosslinked fibers comprising collagen," as claimed. To the contrary, Huang2 considered crosslinking as one possible mechanism to achieve stability but chose instead to blend collagen with PCL.

Ex. 1005, 1791 (“[T]he rapid degradation and poor mechanical properties [of electrospun collagen fibers] determine that either crosslinking or combination with other materials is necessary to obtain a stable scaffold. Electrospinning a blend solution of collagen and polycaprolactone (PCL), a biocompatible and biodegradable synthetic polyester, can yield rather stable nano fibers.”).

64. At the time of invention, a POSITA would have understood that while blending or crosslinking were both known mechanisms to improve the stability of collagen, each had known benefits and disadvantages, and a POSITA would have weighed those competing interests and chosen to *either* blend *or* crosslink but typically would not have done both for reasons explained below. Ex. 1005, 1791.

65. By blending collagen with PCL, Huang² achieved a very stable compound. A POSITA would have known that further crosslinking would have been both unnecessary, given the stability already achieved, and undesirable, given known problems associated with crosslinking. Specifically, a POSITA would have expected a 3:1 PCL/collagen blend like that disclosed by Huang² to be *more* stable than crosslinked collagen because PCL is very hydrophobic and, therefore, degrades very slowly – more slowly than hydrophilic crosslinked collagen. Ex. 2018, Abstract (“long-term degradation (up to 3-4 years)”); Ex. 2021, 376, Fig. 8 (degradation of various collagens over ~2 weeks to >24 weeks). In Huang²’s blend, the extent of water absorption (and, thus, degradation) is dictated by the 3:1 blend

ratio, because the high proportion of PCL present in the blend dictates that less water will be absorbed. A POSITA would not have expected a 3:1 ratio of PCL to collagen to absorb much water at all and, therefore, would have expected a very slow rate of degradation.

66. In contrast, a POSITA would have understood that crosslinked collagen remains hydrophilic and will absorb water much more readily than Huang's 3:1 PCL/collagen blend, leading to more rapid degradation of crosslinked collagen.

67. Given the lower degradation rate of Huang2's PCL/collagen blend, a POSITA would not have further modified Huang2's blended fibers to additionally crosslink them. Doing so would not have been necessary, given the stability already achieved, and would not have imparted additional stability beyond that imparted by blending PCL with collagen. In addition to being unnecessary, a POSITA would not have crosslinked Huang2's blend because this would have introduced to Huang2's process additional cost, complexity, and the very real known drawbacks of crosslinking.

68. For example, cross-linking can both strip away the benefits of using collagen in the first place, such as enhanced biocompatibility and can introduce difficulties in removing the toxic cross-linking chemicals, which pose additional risks. Dr. Simpson himself has expressed these concerns, stating that "[c]ross-linking ... may compromise biocompatibility" and "be cytotoxic because of the

reactive moieties that are covalently coupled between neighboring collagen fibrils.” Ex. 2020, 1594 (explaining that cross-linking electrospun collagen risks “los[ing] their nanofibrous morphology, which is one of the most important features of the scaffold to begin with”). Additionally, glutaraldehyde, “the most commonly used and accepted agent for the cross-linking of biological tissues,” has been “implicated in the development of calcification.” *Id.* Calcification poses a problem for a scaffold like that claimed in the ’227 patent because it imparts detrimental rigidity to the scaffold, which is inappropriate when repairing tendon, ligament, or nerve defects, as claimed, where those tissues each require a certain compliance to function properly. “To avoid” these disadvantages, Dr. Simpson’s “laboratory has previously electrospun blends of collagen with synthetic polymers, which has proven successful in initial cell studies.” *Id.* This paper continued on to explain that “collagen-only electrospun scaffolds” are desirable for certain applications, such as for “cartilage tissue engineering.” *Id.* However, the claims here are directed only to scaffolds for tendon, ligament, or nerve tissue. *Id.* As such, a POSITA would not have accepted the well-documented drawbacks of crosslinking when Huang2’s scaffold achieved necessary stability via blending.

69. Additionally, crosslinking blended PCL/collagen fibers poses further difficulties. In particular, the presence of PCL limits the extent to which collagen can be crosslinked because PCL slows the diffusion of aqueous crosslinkers into the

fiber due to its hydrophobicity. The diffusivity of a crosslinker depends on the degree of swelling of the fiber, which in turn depends on the hydrophobicity of the fiber. As the PCL content increases, the hydrophobicity of the fiber increases, and its degree of swelling decreases, resulting in a decrease in the diffusivity of the crosslinker. Ex. 2035, 745 (“[A]n increase in the polymer concentration reduces the solute diffusivity.”)

70. Petitioner cites Meniel for the uncontroversial proposition that crosslinking collagen scaffolds can decrease the rate of degradation. Pet. 34. This is certainly true for pure *unblended* collagen, which is the only collagen-based scaffolds discussed in Meniel. *See generally* Ex. 1023, Abstract (analyzing scaffolds made of collagen, cross-linked collagen, silk, and RGD-coupled silk). But, as a POSITA would recognize, that statement does not apply to PCL/collagen blends like Huang2’s, and Meniel does not include any guidance concerning crosslinking a PCL/collagen blend. In fact, both a PCL/collagen blend like Huang2’s and crosslinked pure collagen like Meniel discloses have sufficiently low degradation rates to function as a successful scaffold. Ex. 1005, 1791 (“Electrospinning a blend solution of collagen and polycaprolactone (PCL), a biocompatible and biodegradable synthetic polyester, can yield rather stable nanofibers.”); Ex. 1023, 381 (“This method of chemical cross-linking was shown to decrease the rate of degradation of collagen by two orders of magnitude.”). A POSITA would have seen

no need to further modify Huang2's blend. Crosslinking a sufficiently blended collagen scaffold would not further decrease the rate of degradation.

71. Accordingly, in my opinion, a POSITA would not have been motivated to additionally crosslink Huang2's blend because a further increase in stability was not required. Additional crosslinking would have only served to introduce known cost, complexity, and disadvantages associated with crosslinking including reduced biocompatibility and nanofibrous morphology, toxicity, and calcification.

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

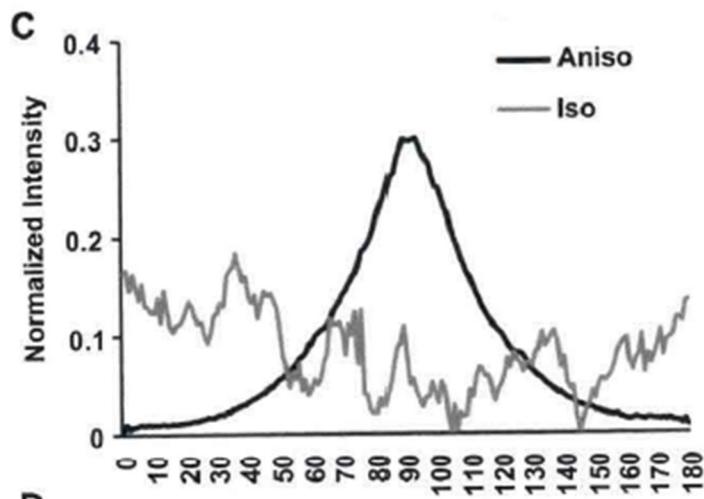
72. In my opinion, Huang2 does not disclose two aspects of this claim: "major ... peaks" and a FFT analysis result having "major adjacent peaks that are about 180° apart from each other."

(1) "major ... peaks"

73. A POSITA would have understood this term to have the definition provided in the Specification, requiring "a height higher than the average height of the peaks in the result." *Supra* § III.D.

74. Huang2 discloses that FFT analysis was performed on aligned and random fibers. Although not used consistently with their ordinary meanings, Huang2 calls the aligned fibers "anisotropic" and the random fibers "isotropic." Ex. 1005, Abstract.

75. Huang2's FFT analysis result is depicted below.



As shown in this FFT result, Huang2 reports that its aligned fibers (Aniso) presented a single peak on FFT analysis.

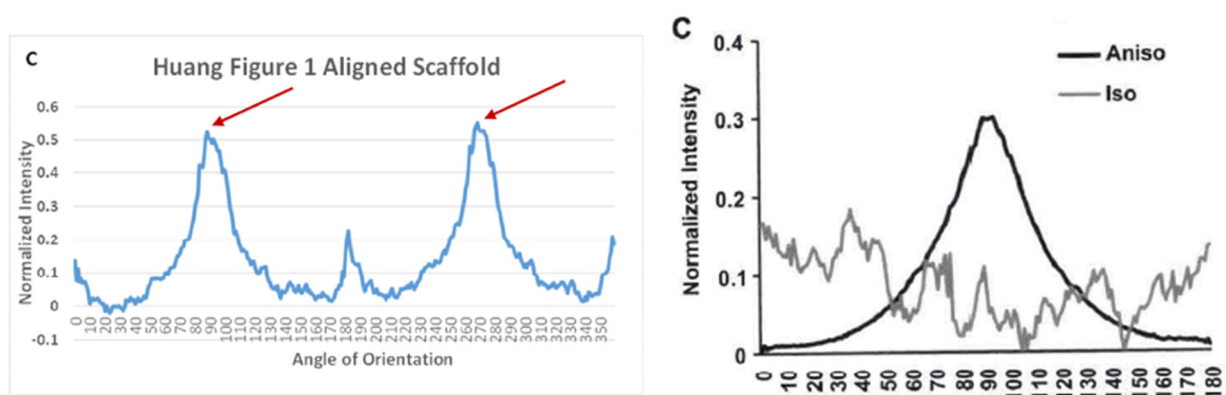
76. To determine the “average [height] of the peaks in the result,” a POSITA would sum the heights of all peaks in the FFT result and divide by the number of peaks (this approach would be the same even if the FFT result were extended to 360°). With a single peak reported by Huang2, and no smaller “minor” peaks, the average height would be the same value as the single peak’s height: 0.3 Normalized Intensity units as shown in the figure above.

77. Therefore, in my opinion, Huang2 does not disclose a “major peak” because the single peak shown above does not have “a height higher than the average of the peaks in the result”—both the depicted peak and the average of all peaks in the FFT analysis have the same height of 0.3 Normalized Intensity units.

78. In my opinion, the post-hoc FFT analysis result that Dr. Simpson

describes to have produced by testing Huang2's image also fails to satisfy this limitation. The FFT analysis result reported by Dr. Simpson conflicts with the FFT analysis result presented by Huang2 itself. Given the conflicting FFT analysis results, a POSITA would not credit the post-hoc testing performed by Dr. Simpson over the authors' own published FFT analysis result.

79. In one area of inconsistency, Dr. Simpson's testing depicts two minor peaks at 0° and 180° that are absent in Huang2. *Compare* Ex. 1003 ¶ 125, with Ex. 1005, Fig. 1C.



80. In the face of such a conflict, a POSITA would credit the Huang2 reference itself and would not credit Dr. Simpson's post-hoc testing, which conflicts with Huang2's disclosure, in part because Huang2 performed more reliable FFT analysis than Dr. Simpson did, for reasons discussed below. *See infra* § IV.B.1.b.2. For example, Dr. Simpson ran FFT on a reproduction of a single SEM image, with a mask applied, while Huang2 ran FFT on five separate and unmasked SEM images. As a result, Huang2 tested a more representative and reliable sample of the scaffold

than Dr. Simpson did. A POSITA would credit Huang2's approach over Dr. Simpson's because Huang2 avoided bias associated with testing only a single area of a much larger scaffold.

81. Additional criticisms of Dr. Simpson's testing are presented below and would have confirmed a POSITA's reliance upon the FFT plot conveyed in Huang2 itself as opposed to the inconsistent plot achieved by Dr. Simpson. *See infra* § IV.B.1.b.2.

(2) “adjacent major peaks with about 180° apart from each other”

82. In my opinion, Huang2 does not anticipate this limitation.

83. Huang2 does not expressly disclose an “adjacent” peak to that shown above in Figure 1C. *See* Ex. 1005. Only a single peak is disclosed.

(a) Lack of reliable testing

84. I understand that Dr. Simpson alleges to have performed FFT testing of Huang2's images. In my view, a POSITA would not credit this testing when interpreting Huang2 because it conflicts with Huang2 and the '227 patent. Additionally, Dr. Simpson does not sufficiently explain this testing. Without an explanation as to how the testing was performed, a POSITA would be unable to evaluate its methodology or credibility and, therefore, would find it unreliable.

(i) Dr. Simpson's testing conflicts with Huang2

85. Dr. Simpson states that his analysis is consistent with “the FFT analysis

described in Huang2 and the '227 patent.” Ex. 1003 ¶ 125. I disagree.

86. Unlike the FFT analysis in Huang2 or incorporated in the '227 patent, Dr. Simpson performed his testing on a photocopy of Huang2's fibers. Dr. Simpson did not test Huang2's SEM images themselves as is customary and accepted in the field.

87. Image quality is the single most important factor in FFT testing and use of high-quality images and equipment is paramount. Poor image quality that lacks sufficient contrast, resolution, and/or brightness results in invalid and inaccurate test results. For example, Dr. Simpson's paper, incorporated into the '227 patent, obtained images “with a Nikon TE300 microscope equipped with a Nikon DXM 1200 digital camera.” Ex. 1010, 607. Likewise, Huang2 examined images “with a LEO 982 FEG SEM.” Ex. 1005, 1792. Without a sufficient image, FFT analysis cannot be credited.

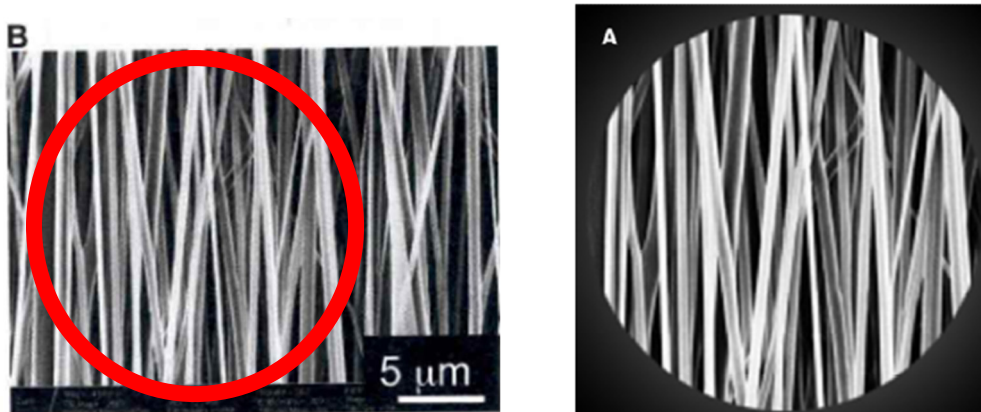
88. A POSITA would not find a reproduced or photocopied image to be suitable for FFT analysis. In fact, I have never performed FFT testing with a reproduced or photocopied image. Reproductions introduce noise, blur, and/or uneven illumination. As a result, image contrast is reduced, and fine details—essential to a reliable FFT result—are lost. These artifacts adversely affect plot shape with high frequency features that reflect fiber orientation most affected and can lead to invalid and inaccurate results.

89. FFT analysis based on photocopied images is too unreliable.

90. Not only did Dr. Simpson perform his testing on an inadequate image, but Dr. Simpson also altered the testing protocol applied by Huang2. Specifically, Huang2 performed FFT analysis on “images of five randomly selected areas” of the scaffold. Ex. 1005, 1792. “Representative SEM images were cropped into a square covering as much of the image as possible.” *Id.* Huang2 then performed FFT analysis “on the SEM images of [the] randomly selected areas ($n = 5$).” *Id.* at 1794. Huang2 did not apply a mask to its images.

91. Unlike Huang2, Dr. Simpson did *not* test images of five randomly selected areas. Instead, Dr. Simpson “cropped and masked” the single image appearing as Huang2’s Figure 1B before applying “2DFFT.”

92. By altering the disclosed protocol, Dr. Simpson performed his testing on an unacceptably small surface area of Huang2’s scaffold. In the image below, I have applied a circle to approximate the position of the mask that Dr. Simpson added to Huang2’s image. As shown below, Dr. Simpson discarded an unacceptable amount of the sole image that he tested.



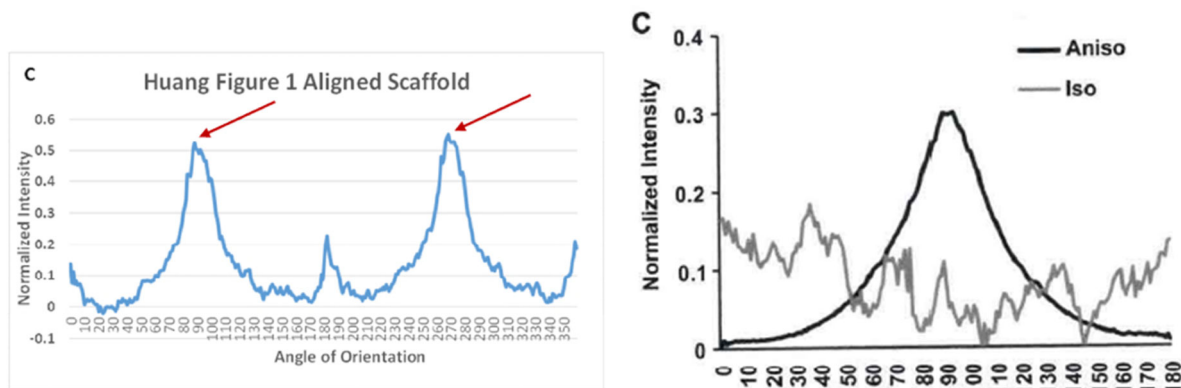
93. I agree with Dr. Simpson's past statements that a POSITA would recognize the importance of testing as much surface area as possible. Ex. 1010, 606 ("[M]easurements of scaffold anisotropy should be averaged over as large an area as possible. Local variations in fiber alignment can bias the 2D FFT process. If necessary, alignment data can be captured from several sites in a scaffold and averaged to circumvent the limitations inherent when a small sample surface area must be used to generate an alignment value."). A POSITA would recognize that Dr. Simpson's testing would produce inaccurate results because he utilized such a small portion in his testing.

94. In addition to unacceptably reducing surface area, Dr. Simpson deviated from Huang2's protocol by applying a mask that Huang2 did *not* apply. Ex. 1005, 1792. This is not a trivial detail. Whether FFT testing includes or excludes a mask greatly impacts the resulting FFT plot. For example, including or excluding portions of the image with a mask will result in different peaks being included or excluded. Dr. Simpson's cited paper discusses one such example, where the

inclusion of a mask removed certain variations present in the FFT plot when created based upon an unmasked image. Ex. 1010, Fig. 3N, 615 (“The unmasked image produces a 2D FFT alignment plot with artifacts in the guise of small peaks on either side of the alignment peaks (Fig. 3N, arrows). Processing the image with a window mask removes this spurious information without altering the height of the alignment peaks (i.e., 2D FFT alignment value, Fig. 3N). Although this type of mask can be useful in many applications, it reduces the total surface area available for analysis.”).

95. FFT analysis results under the different testing protocols will vary, including in the shape and distribution of peaks in the result. For example, the circular selection of the FFT image can affect the outcome of the analysis including changes in the shape of alignment peaks.

96. In fact, the FFT result produced by Simpson’s testing differs from the result reached in Huang2. Compare Ex. 1003 ¶ 125, with Ex. 1005, 1793. These results are reproduced below, side by side.



97. As shown above, Dr. Simpson’s testing produced a markedly different

result than Huang2 (even putting aside that Simpson's testing is plotted to 360).

98. First, Huang2's FFT result depicts a broad curve that extends from 0°–180°. Dr. Simpson's FFT result, however, depicts a much narrower curve, extending at most from 20°–140°. A POSITA would recognize that a broader curve, like Huang2's, reflects fibers that present multiple axes of fiber alignment, while a narrower curve like Dr. Simpson's suggests more limited axes of fiber alignment. *See, e.g.*, Ex. 1010, 610 (“A high and narrow peak indicates a more uniform degree of fiber alignment, a broad peak, or a shoulder on the peak indicates that more than one axis of alignment may be present.”). Given that both sets of FFT results purport to reflect the same set of fibers, this discrepancy alone renders Dr. Simpson's results unreliable.

99. Second, while Huang2's peak reaches a maximum height of 0.3 normalized intensity units, Simpson's peaks extends 83% higher, to 0.55 normalized intensity units. As Dr. Simpson himself acknowledges, a POSITA would understand the height of a FFT peak to be important: “[W]e observe the onset of anisotropic properties in an electrospun scaffold . . . at a threshold alignment value of 0.05 units.^[1] For example, the stress at failure for a random . . . is approximately

¹ Dr. Simpson did not explain the normalization protocol employed in his analysis. Absent such an understanding, a POSITA cannot account for the difference in

0.5 MPa in all directions. Once alignment values of 0.05 units are detected this type of scaffold, stress at failure will increase incrementally as a function of approximately 0.01 2D FFT alignment units.” Ex. 1010, 610. Based upon the reported FFT plots, anisotropic properties like stress at failure for Huang2’s fibers would be notably higher based on Dr. Simpson’s testing (0.5 normalized units) than for Huang2’s reported results (0.3 normalized units). As above, given that both sets of FFT results purport to reflect the same set of fibers from the same image, this discrepancy alone renders Dr. Simpson’s results unreliable.

100. Third, as discussed above, Huang2’s FFT lacks any minor peaks (*see supra* § IV.B.1.b), while Dr. Simpson’s FFT result depicts two smaller peaks at 0° and 180° in addition to the two larger peaks appearing at 90° and 270°. Given that both sets of FFT results purport to reflect the same set of fibers from the same image, this discrepancy alone renders Dr. Simpson’s results unreliable.

101. In sum, these FFT analyses convey fundamentally *different* results and, accordingly, fundamentally *different* information about the underlying fibers.

normalized intensity scale reflected in his testing, at 0.55 units, as compared to his prior paper at 0.05 units. Nonetheless, even on a different unit scale, the same proposition remains: anisotropic properties will increase incrementally as a function of 2D FFT alignment units.

Dr. Simpson does not acknowledge, address, or explain these differences or their impact. Given the deviations Dr. Simpson made in his testing, and the fact that his FFT results differ markedly from those of Huang2, a POSITA would disregard Dr. Simpson's testing. It conflicts with the FFT analysis result from Huang2 and, because Dr. Simpson did not adequately explain his testing protocol, *see infra* § IV.B.1.b.2.a.ii, a POSITA would be unable to interpret and reconcile his data.

(ii) Dr. Simpson's testing protocol is not explained

102. The deviations that Dr. Simpson made as compared to the FFT analysis provided in Huang2 are particularly concerning because Dr. Simpson did not provide a reasonable explanation of how his testing was performed. When conducting FFT analysis, it is customary for a POSITA to document all aspects of their testing such that others may evaluate the test results in view of the protocol employed and, if desired, reproduce those results. Dr. Simpson failed to do so despite acknowledging the importance of various factors to reliable FFT testing.

103. Improperly conducted FFT testing may produce false results. For example, and as discussed above, performing FFT on a reproduced image like Huang2's violates accepted practice and is something I have never done in my practice.

104. Among other important aspects, the circular projection of the image upon which the FFT analysis is performed can also affect the outcome of the

analysis. Ex. 1003 ¶¶ 43-45 (depicting the projection applied to a sample output image). Understanding where the circular projection is placed is a critical aspect of FFT analysis. Specifically, if the circular selection does not capture a representative portion of the FFT output image, it will bias the results. Here, Dr. Simpson did not report where or how he applied the circular projection in the ImageJ software. Without knowing the protocol or steps taken by Dr. Simpson, his results cannot be verified and should not be credited.

105. For example, Dr. Simpson's 2008 paper explains that images should be "stored and analyzed as uncompressed .TIF files to preserve image integrity; the image compression used in .JPG format will degrade image integrity." Ex. 1010, 607. But Dr. Simpson does not address how Huang2's image was stored and/or the impact on his testing. Ex. 1003 ¶¶ 125-126.

106. Additionally, the 2008 paper highlights risks associated with uneven illumination: "Care should be taken at the time of image capture to optimize sample illumination; uneven illumination can complicate and introduce error into the alignment analysis." Ex. 1010, 609. But Dr. Simpson does not address the illumination of the reproduction of Huang2's image that Dr. Simpson tested, instead of testing the actual captured image itself, and/or the impact on his testing. Ex. 1003 ¶¶ 125-126.

107. Moreover, the 2008 paper also explains the impact of optical and

electronic noise on the result, where both sources of noise “can introduce artifacts into a data image and adversely impact the 2D FFT process.” Ex. 1010, 612. Once again, Dr. Simpson does not address whether noise impacted his testing, which type of noise might have been introduced by the applied light intensity, or how he might have accounted for that. Ex. 1003 ¶¶ 125-126.

108. As discussed above, Dr. Simpson appears to have performed his testing based on a reproduction of the images depicted in Huang2. Ex. 1003 ¶¶ 125-126.

109. A POSITA would recognize the importance of this issue. As discussed above, reproductions introduce noise, blur, and/or uneven illumination, where such artifacts adversely affect the resulting FFT plot shape, with high frequency features that reflect fiber orientation being most affected. Dr. Simpson does not establish whether the image presented in Huang2—a reproduction of a scanning electron microscope image obtained from a dated library publication (Pet. 25 n.3)—provides sufficient illumination for testing and to what extent error may have been introduced. Ex. 1003 ¶¶ 125-126; Ex. 1005, 1 (cover page with library sticker). In my view, its resolution is inadequate.

110. Unrecognized in Dr. Simpson’s analysis, the 2008 paper also states that “[n]ormalization is necessary to account for differences in sample thickness, camera performance, operator preference for contrast/brightness, and other variables that impact sample illumination at the time of image capture.” Ex. 1010, 610. While

Dr. Simpson appears to have performed some kind of normalization (*see* Ex. 1003 ¶ 125 (caption, “Normalized intensity values”), Dr. Simpson does not state the extent or mechanism by which that was achieved and any error introduced. Ex. 1003 ¶¶ 125-126.

111. A POSITA would recognize the importance of this issue. Without understanding Dr. Simpson’s normalization protocol, his results cannot be compared to other FFT results and cannot be relied upon. Indeed, as discussed above, although Dr. Simpson normalized his data in some way, it *still* conflicts with that disclosed by Huang2 in peak width, height, and shape.

112. Finally, the 2008 paper explains that although a “mask can be useful in many applications, it reduces the total surface area available for analysis.” As noted above, Dr. Simpson’s testing depicts a mask although Huang2 did not apply one. *See* Ex. 1003 ¶ 125. But Dr. Simpson does not discuss the impact of the mask’s “reduc[tion of] the total surface area available for analysis,” and to what extent that may have affected his testing.

113. A POSITA would recognize the importance of this issue. Indeed, if the reduction of the total surface area imposed by Dr. Simpson’s masking is significant, the result may not be representative of the scaffold.

114. Dr. Simpson’s testing protocol is essentially unknown and, regarding the little that *is* known, it is inconsistent with the FFT approach applied by Huang2.

Absent that explanation, I am unable to sufficiently reproduce this test, and a POSITA would not find Dr. Simpson's testing to be reliable.

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

115. Huang2 discloses that its scaffold is used for skin would repair. *E.g.*, Ex. 1005, Abstract. Huang2 does not disclose repairing tendon, ligament, or nerve defects.

116. In my opinion, a POSITA would not have used Huang2's scaffold to treat tendon, ligament, or nerve defects, even considering Kuo's teachings. Pet. 30, 39-41. This would not have been obvious for at least three reasons, any of which alone would have prevented a POSITA from enacting the proposed combination.

- First, Kuo teaches that treatment of tendon, ligament, or nerve defects requires a rolled scaffold structure that is not present in Huang2. The Petition does not assert that a POSITA would have modified Huang2 to present a rolled structure and, even if Petitioner *had* made such an assertion, a POSITA would not have done so due to well documented problems associated with rolled scaffolds—problems that Dr. Simpson himself described.
- Second, the elastic modulus of Huang2's scaffold—the single most important mechanical property to successful tissue repair—is so disparate from that required to repair tendon, ligament, or nerve that a POSITA would not have expected success in utilizing Huang2's skin repair scaffold to instead repair

tendon, ligament, or nerve tissue. Huang2's scaffold would have been incapable of repairing the claimed tissue types. The Petition does not assert that a POSITA would have modified Huang2 to alter the structure of Huang2's scaffold.

- Third, Kuo's treatment of tendon, ligament, or nerve defects requires seeding the scaffold with the types of cells appropriate for treatment of those specific tissues. By contrast, the scaffold in Huang2 is seeded with fibroblasts, which are incapable of repairing tendon, ligament, or nerve defects. Again, the Petition does not assert that a POSITA would have modified Huang2 to include alternate cell types.

(1) Kuo's Rolled Scaffold

117. In my opinion, it would not have been obvious for a POSITA to utilize the scaffold disclosed in Huang2 to repair tendon, ligament, or nerve tissue because Huang2's scaffold lacks necessary structural elements for repair of those tissue types. The Petition relies on Huang2 and Kuo's common disclosures of the importance of alignment to support this proposed combination. Pet. 39-40. But, as taught by Kuo, repairing tendon, ligament, or nerve tissue requires *more* than an aligned scaffold. Kuo's repair of tendon, ligament, or nerve tissue also requires a scaffold that is rolled in a specific manner to mimic these tissue types. Huang2 presents a non-rolled structure, and the Petition does not identify any reason why a

POSITA would have undertaken to roll it.

118. When treating tendon, ligament, or nerve defects, Kuo utilizes a very specific scaffold structure that is absent in Huang2. Ex. 1018 ¶ 22-23. Kuo teaches repair of tendon, ligament, or nerve defects with a rolled scaffold structure that is specifically created to avoid what Kuo perceives to be defects in two-dimensional scaffolds like Huang2's skin repair scaffold (i.e., poor cell seeding). *Id.* ¶ 112. Specifically, Kuo discloses a specific method to create a three-dimensional, rolled scaffold for treatment of muscle, tendon, ligament, or nerve tissue. *Id.* at Fig. 1 (depicting the process). First, Kuo seeds appropriate cells onto a scaffold. *Id.* ¶ 112. Then, that scaffold is rolled in a "jelly-roll like manner," *id.* ¶ 22, "with the leading edge parallel to the axis of alignment." *Id.* ¶ 112. That "spirally wound tissue construct" is then implanted "into a subject in need of tissue replacement." *Id.* ¶ 22. According to Kuo, this specific rolled structure "mimic[s] the native microstructure of tendon/ligament ... and avoids poor cell seeding ... [which] is a major limitation of aligned scaffolds." *Id.* ¶¶ 112.

119. Kuo explains that its scaffold, "[w]hen seeded with cells and subsequently rolled into cylindrical form[,] ... can be used to form structures e.g., similar to fascicles of the muscle, tendon, nerve, or ligament.... When grouped together, these fascicular-like constructs will represent tissue constructs that when cultured in vitro or implanted in vivo will support cell adhesion, growth and

regenerate tissues.” *Id.* ¶¶ 5-6, Fig. 1 (depicting single rolled scaffold), Fig. 2 (depicting three rolled scaffolds grouped together within a sheath). Although Kuo’s rolled scaffold mimics the structure of muscle, tendon, nerve, and/or ligament fascicles, that rolled structure *does not* mimic two-dimensional skin tissue, for which Huang2’s scaffold is designed. Likewise, Huang2’s scaffold mimics the structure of skin, but does not mimic three-dimensional tendon, ligament, or nerve fascicles, for which Kuo’s scaffold is designed.

120. To the contrary, the skin repair performed with Huang2’s scaffold requires the two-dimensional structure disclosed by Huang2, because it mimics the anatomy of skin tissue which is to be repaired. A POSITA would not have attempted to repair two-dimensional skin tissue with Kuo’s three-dimensional rolled structure because that rolled structure does not mimic native skin tissue. Likewise, a POSITA would not have attempted to repair three-dimensional tendon, ligament, or nerve fascicle tissue with Huang2’s two-dimensional structure because that two-dimensional structure does not mimic native tendon, ligament, or nerve fascicles. Nor would a POSITA have expected success.

121. In support of its proposed combination of Huang2 and Kuo, the Petition argues that a POSITA would have used Huang2’s scaffold with aligned fibers to treat nerve, ligament, or tendon tissue because Kuo recognizes the desirability of using aligned fibers to mimic these native tissues, where those native structures

include aligned fibers. Pet. 39-40. But Petitioner misreads Kuo’s disclosure. In repairing these tissues, Kuo relies upon its rolled structure; aligned fibers are certainly utilized in some embodiments but that is an optional and secondary feature of Kuo’s disclosure. In fact, Kuo explains that its fibers may alternatively be aligned, random, or a combination thereof. *See, e.g.*, Ex. 1018 ¶¶ 5, 12, 34. But when repairing tendon, ligament, or nerve tissue, Kuo discloses only a rolled scaffold.

122. The Petition does not propose modifying Huang2’s scaffold to utilize a rolled structure. Even if it had, a POSITA would not have done so. In addition to being ill-suited to skin tissue repair—the sole purpose to which Huang2 is drawn—a POSITA would have recognized several prohibitive drawbacks associated with rolled scaffolds. For example, it was well known that thin, flat electrospun scaffolds like Huang2’s generally allow good survival for the seeded cells due to sufficient exposure to essential nutrients and oxygen. However, when rolled into thicker constructs, diffusion limitations occur, leading to cell death in the core of the scaffold. Ex. 2023, 145 (explaining that cells cultured in a spinner flask “experienced the convective forces generated by the rotation of the magnetic stirrer in the bottom of the flask” and “[a]lthough the media volume is 120 mL, the cells experienced in their direct vicinity a small fraction of the media. If the rate of nutrient consumption from the immediate vicinity of the cells is faster than the replacement rate of that nutrients then a nutrient concentration gradient is generated

on the scaffold's surface and the seeded cells may experience malnutrition or decreased concentrations of growth factors vital for their growth and differentiation.”).

123. Petitioner's expert, Dr. Simpson, recognizes additional deficiencies when using rolled structures, all of which would have been known to a POSITA and would have prevented a skilled artisan from rolling Huang2's scaffold. Ex. 2022. These deficiencies associated with rolling include:

- “Other attempts at making nerve guides from electrospun (and other) types of fibers generally involve rolling sheets of material to form tubes. Unfortunately, the resulting tubes are *hollow and thus fail to mimic the architecture of natural nerve growth.*” *Id.* at 3:54-58 (emphasis added).
- “Further, a flat sheet that is rolled into a tube must, of necessity, have ‘seams’ where the edges of the rolled sheets are surface exposed ... *resulting in discontinuities and possible weak connective points* in the structure.” *Id.* at 3:58-63 (emphasis added); *see also id.* at 5:39-46 (explaining that axons “cluster and grow as a *jumbled disorganized mass* along the seams” which is “associated with reduced axon targeting”) (emphasis added).
- “In attempts to produce a more autologous graft-like structure aligned

sheets of electrospun materials and films have been prepared and rolled tightly into more compact structures. (The final construct resembles a cinnamon breakfast roll....). While these structures are composed of ‘aligned fiber arrays *even these structures contain large seams* (with respect to the size of the axons), no matter how tightly they may be rolled during fabrication. *These seams represent a potential nexus for mechanical failure and the infiltration by unwanted interstitial fibroblasts and or inflammatory cells.*” *Id.* at 3:63-4:8 (emphasis added); *see also id.* at 31:66-32:3.

124. In my opinion, a POSITA would not have utilized Huang2’s scaffold to treat tendon, ligament, or nerve tissue, even when considering Kuo’s teachings, because Kuo explains that repair of these tissues requires a rolled structure that Huang2 lacks. Indeed, if a POSITA desired to treat nerve, ligament, or tendon tissue, Kuo discloses a rolled scaffold to achieve that aim. I see no reason why a POSITA would instead attempt to repair these tissues with Huang2’s non-rolled scaffold when Kuo relies on this rolled structure so explicitly.

(2) Variations in Stiffness and Elastic Modulus

125. In my opinion, it also would not have been obvious for a POSITA to utilize the skin-repair scaffold disclosed in Huang2 to repair tendon, ligament, or nerve tissue because the elastic modulus of Huang2’s scaffold would have been

entirely unsatisfactory for repair of tendon, ligament, or nerve tissue. A POSITA would not have expected success.

126. The elastic modulus under tension (or tensile elastic modulus) is the most important mechanical property for tissue repair. Elastic modulus is a measurement of a material's stiffness that, in essence, reflects that material's resistance to deformation by an applied force. A higher elastic modulus indicates a stiffer material, while a lower value indicates a more flexible and compliant material.

127. When developing engineered tissue scaffolds like that in the '227 patent, it is critical that the scaffold mimic the stiffness of the native tissue to be repaired. This is because seeded stem cells will differentiate into specific tissues based on mechanical properties of the tissue scaffold, like elastic modulus. Ex. 2024, Abstract ("Naive mesenchymal stem cells (MSCs) are shown here to specify lineage and commit to phenotypes with extreme sensitivity to tissue-level elasticity."). This is essential for cell growth and tissue regeneration, via adhesion, proliferation, and differentiation. A scaffold whose elastic modulus is properly matched to native tissue influences how the cells respond and is determinative in the success of tissue repair.

128. In tissue repair, seeded stem cells sense the mechanical responsiveness of the scaffold and differentiate into tissues with mechanical properties like those of the scaffold. Ex. 2024, Abstract ("Soft matrices that mimic brain are neurogenic,

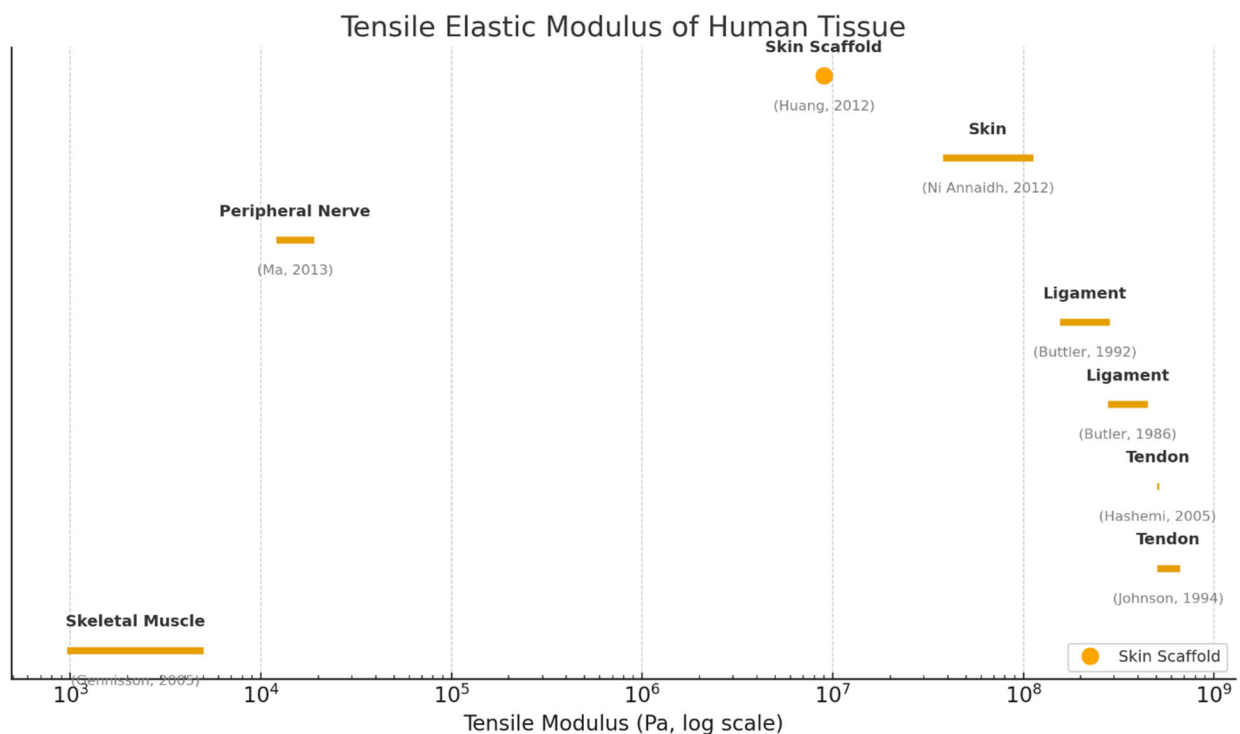
stiffer matrices that mimic muscle are myogenic, and comparatively rigid matrices that mimic collagenous bone prove osteogenic.”). For example, stem cells cultured on a scaffold with an elastic modulus similar to that of bone tissue will differentiate into bone cells. *Id.*

129. The table and graph below summarize known ranges of tensile elastic moduli for the tissues relevant to this asserted ground of unpatentability. To be sure, there is variability in reported elastic modulus values depending on the precise tissue type, relative anisotropy, and donor factors, among others, but the values reflected below are well established in the art.

<u>Tissue</u>	<u>Elastic Modulus (MPa)</u>	<u>Reference</u>
Skeletal Muscle (human) ²	0.00096-0.00501	Ex. 2025, Gennisson, J. Biomechanics, 2005 at 1548
Tendon (Patellar, human)	504-660	Ex. 2026, Johnson, J. Orthop. Res., 1994 at 801
Tendon (Patellar, human)	501.4-513.4	Ex. 2027, Hashemi, Clinical Biomechanics, 2005 at 649

² In Gennisson, shear modulus was reported. I calculated the elastic modulus values reported above using the approximation $E=3G$, where E is tensile elastic modulus and G is shear modulus. This approximation is generally accurate for incompressible materials, such as human tissues (which are incompressible because they consist mostly of water). See, e.g., Properties of Water, available at https://en.wikipedia.org/wiki/Properties_of_water.

Ligament (knee, human)	278-447	Ex. 2028, Butler, J. Biomechanics, 1986 at 429
Ligament (knee, human)	155-284	Ex. 2029, Butler, J. Biomechanics, 1992 at 511
Peripheral Nerve (human)	0.012-0.019	Ex. 2030, Ma, J. Biomed. Mater. Res. Part A, 2013 at 2722
Skin (human)	37.66-112.47	Ex. 2031, Ni Annaidh, J. Mech. Behav. Biomed. Mater., 2012 at 145
Skin Scaffold (engineered; aligned)	8.98	Ex. 1005, Huang ² , Biomaterials, 2012 at 1794



130. As shown above, the tensile elastic modulus values for skin, tendon, ligament, and nerve tissues are highly varied relative to each other. For example, skin tissue has an elastic modulus value much lower than that for tendon or ligament. Skin tissue ranges from 37 – 112 MPa, while tendon tissue may reach up to 660 MPa

and ligament up to 447 MPa. By contrast, the elastic modulus value of nerve tissue, which ranges from 0.012 to 0.019 MPa, is notably lesser than that of skin tissue.

131. Knowing these differences, a POSITA would not have used a skin scaffold like Huang2's, with an elastic modulus of 8.98 MPa (Ex. 1005, 1794), to repair tendon or ligament tissue. Tendon and ligament tissue have elastic moduli reaching 660 MPa and 447 MPa, respectively. Given these drastic differences in stiffness, Huang2's scaffold would be entirely insufficient to perform the functions required by tendon and ligament, which are very stiff load-bearing tissues. In other words, a POSITA would not have selected Huang2's scaffold to repair these tissues because it is up to 73 times less stiff than required (comparing Huang2's 8.98 MPa to the 660 MPa of tendon, i.e., $660 \div 8.98 = 73.5$).

132. Likewise, a POSITA would not have used Huang2's skin tissue scaffold, with its elastic modulus of 8.98 MPa (Ex. 1005, 1794), for nerve repair, where nerve tissue has an elastic modulus of 0.012-0.019 MPa, because nerve tissue requires a 472.6 times lower elastic modulus (comparing Huang2's 8.98 MPa to the 0.019 MPa of nerve, i.e., $8.98 \div 0.019 = 472.6$). Huang2's skin scaffold would impart too much stiffness, which would hinder effective nerve repair.

133. When comparing the maximum elastic modulus for the tissues referenced above against Huang2's scaffold, the following conclusions can be reached:

- The elastic modulus of tendon (660 MPa) is 73.50 times higher than that of Huang2's scaffold, such that Huang2's scaffold is too compliant to successfully repair tendon tissue.
- The elastic modulus of ligament (447 MPa) is 49.78 times higher than Huang2's scaffold, such that Huang2's scaffold is too compliant to successfully repair ligament tissue.
- The elastic modulus of nerve (0.019 MPa) is 472.6 times lower than Huang2's scaffold such that Huang2's scaffold is too stiff to successfully repair nerve tissue.

(3) Kuo's Cell Seeding and Scaffold Structure

134. In my opinion, it also would not have been obvious for a POSITA to utilize the scaffold disclosed in Huang2 to repair tendon, ligament, or nerve tissue because Huang2's scaffold lacks necessary structural elements for repair of those tissue types. The Petition relies on Huang2 and Kuo's common disclosures of the importance of alignment to support this proposed combination. Pet. 39-40. But repairing tendon, ligament, or nerve tissue requires *more* than an aligned scaffold. The scaffold must be specifically tailored to repair the desired tissue type. Huang2 is tailored only to repair skin tissue.

135. Because the scaffolds disclosed by Huang2 are designed to repair skin tissue, they are seeded with specific cells to achieve that function, i.e., normal human

dermal fibroblasts (“NHDF”). Ex. 1005, 1791. NHDF are cells isolated from the human dermis (the layer of skin below the epidermis) that are used in tissue engineering applications to facilitate skin wound healing. *See id.* NHDFs are *not* typically used to repair tendon, ligament, or nerve tissue because other types of cells are more particularly targeted to those tissue types. For example, tenocytes, ligamentocytes, and Schwann cells are commonly used to repair these tissues.

136. Every type of specifically differentiated cell type is associated with the growth or repair of an associated tissue type. Alternatively, stem cells and/or progenitor cells may be used for tissue repair of various tissue types because those cells further differentiate into specific cell types, as determined by the appropriate environmental conditions and the mechanical responsiveness of the scaffold material. Regardless, in all cases, the type of cell and the scaffold environment in which the cell is seeded dictates the precise tissue type that will be repaired or regenerated. Kuo recognizes this, stating that different cell types will be used “depending upon the intended function of the tissue engineered construct.” Ex. 1018 ¶ 58.

137. A POSITA would not expect success in repairing a specific tissue type with a scaffold that is seeded with a *different* type of differentiated cell. For example, a POSITA would not have expected success in repairing tendon, ligament, or nerve tissue with Huang2’s scaffold that is seeded with NHDF because NHDF cells do not

generate tendon, ligament, or nerve tissue—they generate skin tissue. In fact, the specific cells that generate tendon, ligament, or nerve tissue, e.g., tenocytes, ligamentocytes, and Schwann cells, are absent from Huang2.

138. Other environmental and structural factors are also essential for successful tissue repair with a cell-seeded scaffold. The mechanical properties of the scaffold substrate must be calibrated to the tissue type that will be repaired in terms of, among others, scaffold stiffness (as discussed above regarding elastic modulus) and scaffold degradation rate. In that regard, a POSITA would expect the skin-repair scaffold disclosed by Huang2 to possess a relatively low stiffness level that matches skin tissue, while a POSITA would expect Kuo's tendon-repair scaffold to possess a notably more rigid structure to match the tendon tissue that is being repaired. *See supra* § IV.B.1.c.2 (discussing the importance of stiffness, i.e., elastic modulus).

139. Likewise, the rate at which the scaffold degrades must be controlled to match the rate of new tissue formation. This is typically controlled through the addition of specific polymers to the scaffold to control degradation, as discussed above regarding Huang2's election to blend collagen with PCL to achieve stability.

140. A POSITA would have known that skin tissue is regenerated at a notably different rate than tendon, ligament, or nerve tissue because different tissues secrete extracellular matrix (ECM) at different rates. Secreted ECM provides

structural support to newly formed tissue and, therefore, the scaffold degradation rate must generally match the native rate of ECM secretion. Accordingly, a POSITA would have expected Huang2's and Kuo's scaffolds to employ different ratios of polymers to appropriately control the rate of degradation to match the appropriate rate of ECM secretion for each different tissue type. For example, a POSITA would have understood that the tissue regeneration rate of skin is much faster than that of muscle, nerve, ligament, or tendon because of the abundance of stem cells and the richness of blood supply that is present in skin as compared to muscle, nerve, ligament or tendon.

141. For these reasons, the scaffold cell seeding and mechanical properties that are suitable for skin repair are not the same as those suitable for repair of tendon, ligament, or nerve tissue. Accordingly, a POSITA would have recognized that Huang2's scaffold would not be successful if used to repair tendon, ligament, or nerve tissue, as taught by Kuo, because of important structural differences, including the seeded cell type (NHDF), the scaffold's mechanical properties like stiffness, and the scaffold's degradation rate.

142. The Petition does not propose altering Huang2's scaffold to modify the type of cells seeded on the scaffold or any other essential scaffold characteristic like stiffness or degradation rate. Even if it had proposed such a modification, this would not have been obvious to a POSITA who would have recognized that calibrating the

appropriate conditions for tissue repair requires tailoring of factors that are not accounted for in the Petition.

d) Dependent claims 2-6

143. Because claims 2-6 depend, directly or indirectly, from claim 1, I understand that they incorporate all limitations of claim 1. In my opinion, Petitioner has not shown that these dependent claims would have been obvious over Huang2 and Kuo at least because, as described above, Huang2 and Kuo do not satisfy claim 1. *See supra* § IV.B.1.

2. Claim 2

144. Claim 2 depends on claim 1 and recites that “the scaffold is in the form of one or more elongated sheets.” Ex. 1001, 23:38–39. In my opinion, Huang2 and Kuo do not render obvious this claim.

145. A POSITA would have understood the term “sheet,” as used in this claim, in a manner consistent with its ordinary meaning as something that is substantially thinner in one dimension than in all other dimensions. Ex. 2032, S22 (defining as “2. A flat, thin anatomic structure or tissue.”); Ex. 2033, 1632 (defining as “1. a rectangular piece of cotton, linen, etc., for a bed covering. 2. Any structure resembling such a covering”).

146. As discussed above, *see supra* § IV.B.1.c, a POSITA would have understood the proposed combination of Huang2 and Kuo to require a jelly-roll type

scaffold because Kuo indicates that its rolled structure is essential to its repair of tendon, ligament, or nerve defects, for the scaffold to mimic those structures. A POSITA would not have understood a scaffold that “is spirally wound in a jelly-roll like manner” like Kuo’s, Ex. 1018 ¶ 7, to be “in the form of one or more elongated sheets” because that rolled structure is not flat, thin, or substantially thinner in one dimension than in all other dimensions. A POSITA would have expected a sheet to generally lay flat, which a rolled scaffold does not and cannot.

3. Claim 3

147. Claim 3 depends on claim 1 and recites that “the scaffold is a composite of multiple layers of one or more sheets.” Ex. 1001, 23:40–41. In my opinion, Huang2 and Kuo do not render obvious this claim.

148. A POSITA would not have understood Kuo to teach multiple layers of one or more sheets. Although Kuo selectively uses the term “sheets,” Kuo does so only in describing different shapes its scaffold might take, all in the plural form. Ex. 1018 ¶ 24. When describing the scaffolds, Kuo does not describe scaffolds with multiple layers of sheets.

149. As discussed above, *see supra* § IV.B.1.c, a POSITA would have understood the proposed combination of Huang2 and Kuo to require a jelly-roll type scaffold. That structure does not include multiple layers that are flat, thin, or substantially thinner in one dimension than in all other dimensions. Ex. 2032, S22;

Ex. 2033, 1632. A POSITA would have expected multiple layers of sheets to generally lay flat, which a rolled scaffold does not and cannot.

150. A POSITA would have seen no advantage in rolling multiple sheets. Indeed, as discussed above, it was well understood that rolling a scaffold creates issues including difficulty in the diffusion of nutrients toward the center of the rolled scaffold, seams, and weak connective points. Ex. 2022, 3:54-63, 5:39-46; Ex. 2023, 145. Including multiple layers in such a rolled scaffold would only exacerbate these difficulties. Accordingly, a POSITA would not have found this to be obvious.

4. Claim 4-6

151. Claims 4, 5, and 6 depend on claim 1 and further recite that “the tissue defect is” a nerve defect, ligament defect, or tendon defect, respectively. Ex. 1001, 23:38–39. My opinions outlined above, *see supra* § IV.B.1.c, apply equally to these claims.

C. Ground 2: Alleged Obviousness over Lee and Kuo

152. In my opinion, Lee and Kuo do not render obvious claims 1-6.

1. Claim 1

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

153. In my opinion, Lee does not disclose this limitation.

154. Lee does not expressly disclose FFT analysis at all and, therefore, does not disclose the claimed FFT analysis result. *See* Ex.1011.

155. I have reviewed the Petition's arguments regarding this ground, and I am unable to identify any argument by Petitioner that Lee's fibers inherently present a FFT analysis result that necessarily demonstrates "adjacent major peaks with about 180 apart from each other." Pet. 47-51.

156. As explained above in Section II.B, I understand that inherency requires a showing that the prior art necessarily includes the claim element but that it is not enough to show that the claim element is merely possible or probable. Instead, the limitation must be necessarily present in all circumstances. By my reading, the Petition does not make this showing because it simply argues that FFT analysis could be performed and, if it was, that the FFT analysis would show that "the fibers were oriented on the scaffold in Lee in an aligned manner." Pet. 50. But fibers being oriented in an aligned manner is not an element of the claims nor does the Petitioner argue that the claim language would necessarily be present.

157. The Petition argues that Lee confirmed fiber alignment in several ways including through SEM analysis and ImageTool 3.0 freeware analysis. Pet. 48. The Petition argues that a POSITA "would know that the degree of alignment could also be determined using ImageJ software to run an 'FFT analysis'." *Id.* at 50. The

Petition states this could have been done “to confirm the of alignment of Lee’s fibers.” *Id.* at 51.

158. I disagree. Lee does not express any doubt regarding the alignment of its fibers. For example, Lee states that fiber morphology was determined with SEM (Ex. 1011 ¶ 65), fiber orientation was determined with ImageTool 3.0 (*id.* ¶ 66), cell alignment was assessed by SEM (*id.* ¶¶ 74, 77), and tensile testing was performed with fibers of different orientations (*id.* ¶¶ 67, 81). In the face of this information, a POSITA would not have invested further resources, time, or money to confirm this information, especially in the absence of any conflicting or contradictory information regarding alignment. A POSITA practicing in this field would seek to be efficient and conserve resources. It would be atypical to invest further time or money to reaffirm information that is already known especially because the time and money spent to reconfirm information is necessarily lost for future investigation. Quite simply, this is now how a POSITA would operate.

(a) Lack of reliable testing

159. I understand that Dr. Simpson alleges to have performed FFT testing of Lee’s images. In my view, a POSITA would not credit this testing when interpreting Lee because it conflicts with the ’227 patent. Additionally, as discussed above regarding Ground 1 (which is incorporated by referenced), Dr. Simpson does not sufficiently explain his testing. Without an explanation as to how the testing was

performed, a POSITA would be unable to evaluate its methodology or credibility and, therefore, would find it unreliable.

(i) **Dr. Simpson's testing conflicts with the '227 patent**

160. Dr. Simpson states that his analysis is consistent with “the FFT analysis described in the '227 patent.” Ex. 1003 ¶ 183. I disagree.

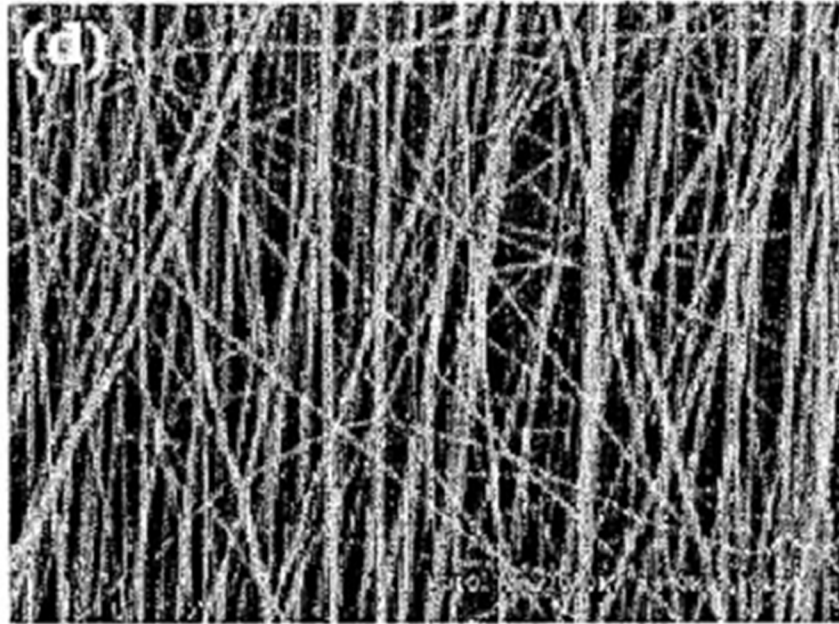
161. Unlike the FFT analysis in the '227 patent, Dr. Simpson performed his testing on a poor-quality photocopy of Lee fibers. Dr. Simpson did not test SEM images themselves as is customary and accepted in the field.

162. As discussed above, image quality is the single most important factor in FFT testing and use of high-quality images and equipment is paramount. Without a sufficient image, FFT results cannot be credited. Poor image quality that lacks sufficient contrast, resolution, and/or brightness results in invalid and inaccurate test results. For example, Dr. Simpson's paper, incorporated into the '227 patent, obtained images “with a Nikon TE300 microscope equipped with a Nikon DXM 1200 digital camera.” Ex. 1010, 607. Likewise, Lee examined images a “Model S-2260N, Hitachi Co. Ltd., Japan” SEM. Ex. 1011 ¶ 65.

163. A POSITA would not find a photocopied image to be suitable for FFT analysis. In fact, I have never performed FFT testing with a photocopied image. Photocopies introduce noise, blur, and/or uneven illumination. As a result, image contrast is reduced, and fine details—essential to a reliable FFT result—are lost.

These artifacts adversely affect plot shape with high frequency features such as small-scale variations that reflect fiber orientation most affected.

164. The image that Dr. Simpson tested is shown below.



Ex. 1003 ¶ 179. In my experience, a POSITA would never conduct FFT analysis on such an image and would not credit results of any FFT analysis performed on such an image because this image includes a remarkable amount of noise and lacks necessary contrast between individual fibers, especially regarding deeper fibers that appear toward the visual background of Lee's image. Absent clear delineation between fibers, especially regarding deeper fibers, the FFT analysis incorrectly analyzes the orientation of the fiber scaffold. This is recognized in Dr. Simpson's earlier work where he stated that FFT analysis of SEM images "must assume a uniform distribution of fibers throughout the cross-sectional diameter of the

scaffold,” when deeper fibers cannot be detected in the SEM image. Ex. 1013, 9.

165. Performing FFT analysis on this reproduction of Lee’s SEM image leads to invalid and inaccurate results especially due to the excessive noise. Dr. Simpson has stated that images, like Lee’s, that are “composed largely of optical noise” are “unsuitable for analysis” with FFT because “individual fibers are not detected.” Ex. 1010, 605. That is the case here where Lee’s image is “unsuitable for analysis” because it contains optical noise that prevents sufficient discernment of the individual fibers and/or edges. One such example is shown below.



Ex. 1003 ¶ 179 (taken from the lower right portion of the image). FFT analysis is useless on such an image because the individual fibers cannot be detected. FFT analysis based on this photocopied image is too unreliable. The reproduced image renders it outside of acceptable levels of resolution.

166. Not only did Dr. Simpson perform his testing on an inadequate image but, to the extent his protocol can be discerned at all, Dr. Simpson altered the protocol applied in the '227 patent.

167. In this field of art, a POSITA recognizes that it is imperative to sufficiently document the applied FFT analysis so others can evaluate the resulting data and reproduce the testing. But here Dr. Simpson’s declaration is apparently

incomplete. Upon reading Dr. Simpson's declaration, a POSITA would believe that he did not apply a mask to Lee's image. For example, when describing his testing of Huang2's image, Dr. Simpson states that he masked the image and shows the mask that he applied, Ex. 1003 ¶ 125, but he does not show or describe any such mask applied to Lee's image. *Id.* ¶ 183.

168. But Dr. Simpson testified during his deposition that he *did* in fact apply a mask to Lee's image. Ex. 2017, 163:4-15. This omitted information is essential. Without knowing where or how Dr. Simpson applied a mask, his FFT analysis cannot be evaluated. For example, is unclear how much of Lee's image was discarded by applying his mask. Moreover, application of a mask is not "the FFT analysis described in the '227 patent." Ex. 1003 ¶ 183. Specifically, the '227 patent incorporates the FFT analysis described in Dr. Simpson's 2008 paper (Ex. 1010), but this paper discloses only an *optional* mask—an option that was not exercised in the '227 patent. *See* Ex. 1001, Fig. 8A (depicting the tested image without a mask).

169. This is not a trivial detail. A POSITA would recognize that inclusion or exclusion of a mask will directly alter the resulting FFT plot. Dr. Simpson's own publication acknowledges that masks alter the resulting FFT plot. Ex. 1010, 615 (explaining that provision of a mask alters the FFT analysis result by eliminating certain peaks).

(ii) **Dr. Simpson's testing protocol is not explained**

170. This lack of transparency in the FFT protocol is insufficient. When performing FFT analysis, it is customary for a POSITA to document all aspects of their testing such that others may evaluate the test results in view of the protocol employed and, if desired, reproduce those results. Dr. Simpson failed to do so despite acknowledging the importance of various factors to reliable FFT testing.

171. As discussed regarding Ground 1, which is incorporated by reference, improperly conducted FFT testing may produce false results. For example, and as discussed above, photocopies introduce noise, blur, and/or uneven illumination, where such artifacts adversely affect the resulting FFT plot shape, with high frequency features such as small-scale variations being most affected. Performing FFT on a photocopied image like Lee's violates accepted practice and is something I have never done in my practice. Likewise, inclusion or exclusion of a mask also directly impacts the FFT results.

172. Moreover, the circular projection of the image upon which the FFT analysis is performed is critical and can directly affect the outcome of the analysis. If the circular selection does not capture a representative portion of the FFT output image, it will bias the results. Here, Dr. Simpson did not report where or how he applied the circular projection in the ImageJ software. Without knowing the protocol or steps taken by Dr. Simpson, his results cannot be verified and should not be credited.

173. Among other things, Dr. Simpson also failed to document the version of software he utilized and how Lee's image was stored.

174. Dr. Simpson's testing protocol is essentially unknown and, regarding the little that *is* known, it is inconsistent with the FFT approach applied in the '227 patent. Absent that explanation, I am unable to sufficiently reproduce this test, further rendering it unreliable.

b) "... and applying the scaffold to the tissue defect to repair a tendon, a ligament or a nerve defect."

175. In my opinion, Lee does not disclose or render obvious this limitation.

176. Lee discloses a scaffold for muscle tissue repair, achieved by seeding Lee's scaffold with human skeletal muscle cells ("hSkMCs"), which "fuse[] and form[] myotubes." Ex. 1011 ¶¶ 2, 31, 60, 72–73, 82. Lee does not disclose repairing tendon, ligament, or nerve defects.

177. A POSITA would not have used Lee's muscle scaffold to repair alternate types of tissues because it is only suitable for muscle repair. This is so even considering Kuo's teachings. As discussed above regarding Ground 1, where those opinions are incorporated here by reference, this would not have been obvious for at least three reasons, discussed below.

(1) Kuo's Rolled Scaffold

178. As discussed above regarding Ground 1, Kuo's treatment of tendon, ligament, and nerve requires a scaffold that is rolled in a unique "jelly-roll like

manner,” Ex. 1018 ¶ 22, which allegedly presents advantages over non-rolled scaffolds like Lee’s (i.e., poor cell seeding). *Id.* ¶ 112. For the same reasons detailed above, a POSITA would not have utilized Lee’s unmodified scaffold to repair tendon, ligament, or nerve because Lee’s scaffold lacks the unique rolled, three-dimensional structure that Kuo specifically employs to mimic the structure of tendon, ligament, or nerve tissues. *Id.* ¶ 5.

179. Although both Lee and Kuo commonly teach muscle tissue repair, Kuo makes clear that its treatment *requires* the unique rolled design. Kuo does not provide any indication that its disclosed muscle repair would have been successful without the rolled structure that Lee lacks. *See, e.g.*, Ex. 1011 ¶ 2; Ex. 1018 ¶ 5 (rolled scaffold is “similar to fascicles of the muscle”). Therefore, in my opinion, although both Lee and Kuo teach muscle repair, they do so by different mechanisms. Given these references’ teachings, a POSITA would not see fit to extend Lee’s muscle-repair teachings to also repair tendon, ligament, or nerve, where Kuo explicitly relies upon a rolled structure to do so.

180. As above, the Petition does not propose modifying Lee to present the rolled structure that is essential to Kuo’s tendon, ligament, or nerve repair. In fact, Lee provides no indication that its scaffold should be rolled. The “shapes” that Lee discloses for its scaffold are thin films, meshes, porous sheets or grafts, and multilayer polymeric matrices. Ex. 1011 ¶ 56. Lee does not disclose rolling the

scaffold with the leading edge parallel to the axis of alignment to create a spiral rolled structure. Ex. 1018 ¶¶ 5, 112.

181. Even had it been proposed, a POSITA would not have found it obvious to roll Lee's scaffold because of the known drawbacks associated with use of rolled scaffolds, discussed above regarding Ground 1 and which apply equally here. *See, e.g.,* Ex. 2022, 3:54-4:9, 5:39-46 (explaining that rolled structures fail to mimic natural nerve growth, contain seams that result in weak connective points, cause axons to grown in a "jumbled disorganized mass," and allow for infiltration by unwanted cells).

182. Accordingly, a POSITA would not have expected success in using Lee's scaffold to repair tendon, ligament, or nerve tissue when Kuo requires a rolled structure that is absent in Lee.

(2) Variations in Stiffness and Elastic Modulus

183. As discussed above regarding Ground 1, the elastic modulus of a tissue repair scaffold must mimic that of native tissue for successful tissue repair. Ex. 2024, Abstract.

184. Unlike Huang2, Lee does not report its scaffold's elastic modulus. In the absence of a specific disclosure, a POSITA would expect the scaffold's elastic modulus to mimic that of the native tissue to be repaired because a close approximation in scaffold stiffness is required for successful cell differentiation into

the desired tissue type. *See, e.g.*, Ex. 2024, Abstract. For muscle tissue, the native tissue's elastic modulus ranges from approximately from 0.00096–0.00501 MPa, and a POSITA would expect a comparable value for a muscle repairing scaffolds. Ex. 2025, 1548; *see supra* ¶ 129.

185. As discussed above, the elastic modulus of tendon and ligament vary markedly from these values for muscle tissue, ranging up to 660 and 447 MPa, respectively. Ex. 2026, 801; Ex. 2028, 429; *see supra* ¶ 129. And that of nerve tissue also varies from that of muscle, ranging from 0.012 to 0.019 MPa. Ex. 2030, 2722; *see supra* ¶ 129.

186. Knowing these differences, a POSITA would not have used a muscle repair scaffold like Lee's, which would be designed to mimic the elastic modulus of native muscle tissue and may be as low as 0.00096 MPa, to repair tendon or ligament tissue. Tendon and ligament tissue have elastic moduli reaching 660 MPa and 447 MPa, respectively. Given these drastic differences in stiffness, Lee's scaffold would be entirely insufficient to perform the functions required by tendon and ligament, which are very stiff load-bearing tissues. In other words, a POSITA would not have selected Lee's scaffold to repair these tissues because tendon and ligament repair require up to *687,500 times* more stiffness than offered by Lee (comparing 0.00096 MPa to the 660 MPa of tendon, i.e., $660 \div 0.00096 = 687,500$).

187. Likewise, a POSITA would not have used Lee's muscle repair scaffold,

with an elastic modulus approximating 0.00096 MPa, for nerve repair, where nerve tissue has an elastic modulus of 0.012-0.019 MPa, because nerve tissue requires *19 times* greater stiffness than offered by Lee (comparing 0.00096 MPa to the 0.019 MPa of nerve, i.e., $0.019 \div 0.00096 = 19.79$). Lee's muscle scaffold would impart too little stiffness, which would hinder effective nerve repair.

188. When comparing the maximum elastic modulus for the tissues referenced above against the approximate elastic modulus of Lee's muscle tissue scaffold:

- The elastic modulus of tendon (660 MPa) is 687,500 times higher than that of Lee's scaffold, such that Lee's scaffold is too compliant to successfully repair tendon tissue.
- The elastic modulus of ligament (447 MPa) is 465,625 times higher than that of Lee's scaffold, such that Lee's scaffold is too compliant to successfully repair ligament tissue.
- The elastic modulus of nerve (0.019 MPa) is 19 times higher than that of Lee's scaffold, such that Lee's scaffold is too compliant to successfully repair nerve tissue.

189. Accordingly, a POSITA would not use a scaffold approximating the stiffness of muscle tissue to repair these alternate tissue types because it would be too compliant to perform the tissue's required functions.

(3) Kuo's Cell Seeding and Scaffold Structure

190. Lee exclusively repairs muscle tissue using scaffolds seeded with human skeletal muscle cells (“hSkMCs”). hSkMCs are unique to muscle but absent in tendon, ligament or nerve tissue. A POSITA would not expect Lee’s scaffold, seeded with hSkMCs, to successfully promote tendon, ligament, or nerve repair because it is devoid of the cell types needed to repair those tissue types. Ex. 1018 ¶ 58 (explaining that different cell types will be used “depending upon the intended function of the tissue engineered construct”).

191. As discussed above regarding Ground 1, the Petition does not explain how, e.g., tendon tissue would have been repaired with Lee’s hSkMCs-seeded scaffold. To the contrary, Kuo demonstrates that when tendon repair is intended, the scaffold is seeded with *tendon* cells (tenocytes) or stem/progenitor cells that differentiate into tendon tissue. Ex. 1018 ¶¶ 16, 112. Nor does the Petition propose modifying Lee’s scaffold to incorporate alternate cell types.

192. As also discussed above, successful tissue regeneration also requires a scaffold matched to that of the target tissue with respect to other mechanical properties such as degradation rate and stiffness. Here, a POSITA would not have expected success in using Lee’s muscle scaffold to repair tendon, ligament, or nerve tissue in the absence of the appropriately matched scaffold mechanical characteristics. As above, a POSITA would have known that muscle tissue is

regenerated at a notably different rate than tendon, ligament, or nerve tissue because different tissues secrete extracellular matrix (ECM) at different rates. Skeletal muscle regenerates at a rapid rate due to its high vascularity and abundance of stem cells. Tendons and ligaments are not as vascularized as skeletal muscle and regenerate more slowly by fibrosis (fibroblast proliferation and extracellular matrix deposition). Peripheral nerve regenerates the slowest by axonal sprouting, depending on nerve length.

193. Accordingly, a POSITA would have recognized that Lee's scaffold would not be successful if used to repair tendon, ligament, or nerve tissue, as taught by Kuo, because of important structural differences, including the seeded cell type (hSkMCs), the scaffold's mechanical properties like stiffness, and the scaffold's degradation rate.

194. The Petition does not propose altering Lee's scaffold to modify the type of cells seeded on the scaffold or any other essential scaffold characteristic like stiffness or degradation rate. Even if it had proposed such a modification, this would not have been obvious to a POSITA who would have recognized that calibrating the appropriate conditions for tissue repair requires tailoring of factors that are not accounted for in the Petition.

(4) Differences in Muscle as Compared to Tendon, Ligament, or Nerve

195. Although Kuo teaches repair of muscle, tendon, ligament, and nerve,

those tissues vary. For example, as discussed above, to ensure successful tissue repair, a scaffold must be appropriately tailored to the desired native tissue type, including with respect to its unique stiffness, degradation rate, and cell seeding. *See supra* § IV.C.1.b.2-3. A POSITA would have recognized that the same scaffold cannot successfully repair each structure absent significant modifications. *E.g.*, Ex. 1018 ¶ 40 (explaining that different methods for making scaffolds will be employed depending on the intended use), 58 (explaining that different cell types will be used “depending upon the intended function of the tissue engineered construct”).

196. A POSITA would recognize that, although Lee and Kuo both teach muscle tissue repair, it does not follow that Lee’s scaffold would have also been used to repair tendon, ligament, or nerve tissue. Indeed, muscle tissue is a highly vascularized tissue, with abundant blood supply, as compared to tendon, ligament, or nerve tissue. Ex. 2034, 301 (“Perivascular cells purified from skeletal muscle or nonmuscle tissues were myogenic in culture and in vivo. Irrespective of their tissue origin, long-term cultured perivascular cells retained myogenicity.... Thus, blood vessel walls harbor a reserve of progenitor cells that may be integral to the origin of the elusive MSCs and other related adult stem cells.”). The low vascularity of tendon, ligament, and nerve tissue affects their regenerative capacity. A POSITA would not have expected success in utilizing Lee’s scaffold to repair tendon,

ligament, or nerve tissue due, in part, to the drastically different vascularization of muscle tissue (which Lee's scaffold is designed to repair) as compared to that of tendon, ligament, or nerve tissue. The scaffold mechanical properties of Lee, its degradation kinetics, and the adhesion, proliferation, and differentiation of the respective cell types would have to be modified to successfully repair tendon, ligament, nerve. The Petition does not address any of these factors.

197. Similarly, Lee is directed to treating large muscle defects, which is often called volumetric muscle loss. *See, e.g.,* Ex. 1011 ¶ 94 (explaining that the “composite nanofiber scaffolds seeded with skeletal muscle cells provides implantable functional muscle tissues for patients with large muscle defects”). This type of large muscle defect usually occurs after trauma, surgery, or infection and involves loss of tissue mass, not just a simple tear. As such, tissue *replacement* is typical.

198. The most common clinically recognized tendon or ligament defects that a scaffold may be used to repair present as acute tears or ruptures or degenerative micro-tearing (e.g., chronic tendinopathy). True segmental loss, of the type that may occur in muscle and to which Lee is directed, is significantly less common unless caused by major trauma or surgical resection. Nerve injuries are also most often described as lacerations, transections, or crush injuries. Clinically, a defect often means a gap (loss of continuity), which results from a tear/transection.

199. In sum, Lee’s scaffold is designed to treat large, volumetric muscle loss and is not adapted to treat the types of tendon, ligament, or nerve injuries that a POSITA would have expected to encounter.

c) Dependent claims 2-6

200. Because claims 2-6 depend, directly or indirectly, from claim 1, I understand that they incorporate all limitations of claim 1. In my opinion, Petitioner has not shown that these dependent claims would have been obvious over Lee and Kuo at least because, as described above, Lee and Kuo do not satisfy claim 1. *See supra* § IV.C.1.

2. Claim 2

201. Claim 2 depends on claim 1 and recites that “the scaffold is in the form of one or more elongated sheets.” Ex. 1001, 23:38–39. In my opinion, Lee and Kuo do not render obvious this claim.

202. A POSITA would have understood the term “sheet,” as used in this claim, in a manner consistent with its ordinary meaning as something that is substantially thinner in one dimension than in all other dimensions. Ex. 2032, S22; Ex. 2033,1632.

203. As discussed above and incorporated herein, *see supra* § IV.C.1.b.1, a POSITA would have understood the proposed combination of Lee and Kuo to require a jelly-roll type scaffold because Kuo indicates that its spirally rolled

structure is essential to its use in repairing tendon, ligament, or nerve defects because it mimics the fascicles of those tissues.

204. A POSITA would not have understood a scaffold that “is spirally wound in a jelly-roll like manner,” Ex. 1018 ¶ 7, like Kuo’s, to be “in the form of one or more elongated sheets” because it is not substantially thinner in one dimension than in all other dimensions. A POSITA would have expected a sheet to lay generally flat, which a rolled scaffold does not and cannot.

3. Claim 3

205. Claim 3 depends on claim 1 and recites that “the scaffold is a composite of multiple layers of one or more sheets.” Ex. 1001, 23:40–41. In my opinion, Lee and Kuo do not render obvious this claim.

206. A POSITA would not have understood Kuo to teach multiple layers of one or more sheets. Although Kuo selectively uses the term “sheets,” Kuo does so only in describing different shapes its scaffold might take, all in the plural form. Ex. 1018 ¶ 24. When describing its scaffolds, Kuo does not describe scaffolds with multiple layers of sheets.

207. As discussed above, *see supra* § IV.C.1.b.1, a POSITA would have understood the proposed combination of Lee and Kuo to require a jelly-roll type scaffold. That structure does not include multiple layers that are flat, thin, or substantially thinner in one dimension than in all other dimensions. Ex. 2032, S22;

Ex. 2033, 1632. A POSITA would have expected multiple layers of sheets to generally lay flat, which a rolled scaffold does not and cannot.

208. A POSITA would have seen no advantage in rolling multiple sheets. Indeed, as discussed above, it was well understood that rolling a scaffold creates issues including difficulty in the diffusion of nutrients toward the center of the rolled scaffold, seams, and weak connective points. Ex. 2022, 3:54-63, 5:39-46; Ex. 2023, 145. Including multiple layers in such a rolled scaffold would only exacerbate these difficulties.

4. Claim 4-6

209. Claims 4, 5, and 6 depend on claim 1 and further recite that “the tissue defect is” a nerve defect, ligament defect, or tendon defect, respectively. Ex. 1001, 23:38–39. My opinions outlined above, see *supra* § IV.C.1, apply equally to these claims.

D. Ground 3: Alleged Anticipation by Huang2

210. In my opinion, Huang2 does not anticipate claims 7-8.

1. Claim 7

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

211. This limitation of independent claim 7 is substantially identical to language in claim 1. My analysis of Huang2’s failure to disclose this limitation, set

forth above, applies identically here and is incorporated by reference. *See supra* § IV.B.1.b.

212. For these reasons, it is my opinion that Huang2 does not anticipate this claim.

2. Claim 8

213. Because claim 8 depends directly on claim 7, I understand that it incorporates all limitations of claim 7. In my opinion, Petitioner has not shown that this dependent claim is anticipated by Huang2 at least because, as described above, Huang2 does not anticipate claim 7. *See supra* § IV.D.1.

V. CONCLUSION

214. For the reasons presented above, it is my opinion that Petitioner has not demonstrated the unpatentability of the challenged claims.

215. In signing this declaration, I recognize that it will be filed as evidence in IPR2025-00249 before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I recognize that I may be subject to cross-examination in this case and that cross-examination will take place in the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

216. I reserve the right to supplement my opinions in the future and to consider new information as it becomes available to me.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

10/28/2025



Date: _____

Antonios G. Mikos, President

Biomedical and Informatics

Consultants, Inc.

APPENDIX A – MATERIALS CONSIDERED

Paper Number	Description
2	Petition for <i>Inter Partes</i> Review of U.S. Patent No. 11,318,227
8	Patent Owner's Preliminary Response
13	Decision Granting Institution of <i>Inter Partes</i> Review

Exhibit Number	Description
1001	U.S. Patent No. 11,318,227 to Francis et al.
1002	'227 Patent Prosecution History
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) (available online Dec. 2, 2011)
1006	Kumbar et al., <i>Electrospun nanofiber scaffolds: engineering soft tissues</i> , Biomed. Mater. 3 (2008)
1007	U.S. Patent No. 10,137,223 Prosecution
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)
1009	U.S. Patent App. Pub. No. 2004/0037813 to Simpson et al.
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)
1011	Lee et al., U.S. Patent Application No. US 2010/0331980 A1, Pub. Date December 1, 2011
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)
1015	Jose et al, <i>Fabrication and Characterization of Aligned Nanofibrous PLGA/Collagen Blends as Bone Tissue Scaffolds</i> , 50 Polymer 3778-85 (2009)
1016	Fu et al, <i>Spatial Arrangement of Polycaprolactone/Collagen Nanofiber Scaffolds Regulates the Wound Healing Related</i>

	<i>Behaviors of Human Adipose Stromal Cells</i> , 18(5) Tissue Engineering, 631-42 (2012)
1018	Kuo et al., U.S. Patent Application No. US 2011/0293685 A1, Pub. Date Dec. 1, 2011
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
1022	McClure et al, <i>Tri-Layered Vascular Grafts Composed of Polycaprolactone, Elastin, Collagen, and Silk: Optimization of Graft Properties</i> , 10 J. Mechanical Behavior Biomedical Materials 48 (2012)
1023	Meinel et al., <i>Engineering Cartilage-Like Tissue Using Human Mesenchymal Stem Cells and Silk Protein Scaffolds</i> , 88(3) Biotechnology Bioengineering 379 (2004)
2003	Dorland's Illustrated Medical Dictionary (29th ed. 2000) – “progenitor”
2004	Dorland's Illustrated Medical Dictionary (29th ed. 2000) – “stem c[ell]”
2016	<i>Curriculum Vitae</i> of Dr. Antonios G. Mikos, Ph.D.
2017	Transcript of October 7, 2025 Deposition of Dr. David Simpson
2018	Woodruff et al., <i>The return of a forgotten polymer- Polycaprolactone in the 21st century</i> , 35 Progress in Polymer Science 1217-1256 (2010)
2019	Zeugolis et al., <i>Electro-spinning of pure collagen nano-fibres — Just an expensive way to make gelatin?</i> , 29 Biomaterials 2293-2305 (2008)
2020	Barnes et al., <i>Cross-Linking Electrospun Type II Collagen Tissue Engineering Scaffolds with Carbodiimide in Ethanol</i> , Tissue Engineering (Vol. 13) 1593-1605 (2007)

2021	Rothamel et al., <i>Biodegradation of differently crosslinked collagen membranes: an experimental study in the rat</i> , 16 Clin. Oral Impl. Res. 369-378 (2005) (“Rothamel”)
2022	U.S. Patent No. 9,572,909 to Simpson, et al., entitled “Electrospun nerve guides for nerve regeneration designed to modulate nerve architecture”
2023	Sikavitsas, et al., <i>Formation of three-dimensional cell/polymer constructs for bone tissue engineering in a spinner flask and a rotating wall vessel bioreactor</i> , J. Biomed. Mater. Res., 62, 136-148 (2002) (“Sikavitsas”)
2024	Engler, et al., <i>Matrix elasticity directs stem cell lineage specification</i> , Cell 126, 677-689 (2006) (“Engler”)
2025	Gennison, et al., <i>Human muscle hardness assessment during incremental isometric contraction using transient elastography</i> , 38 J. Biomechanics, 1543-1550 (2005) (“Gennison”)
2026	Johnson, et al., <i>Tensile and Viscoelastic Properties of Human Patellar Tendon</i> , J. of Orthopaedic Research, 796-803 (1994) (“Johnson”)
2027	Hashemi, et al., <i>The mechanical properties of human patellar tendon are correlated to its mass density and are independent of sex</i> , 20 Chemical Biomechanics, 645-652 (2005) (“Hashemi”)
2028	Butler, et al., <i>Comparison of Material Properties in Fascicle-Bone Unites from Human Patellar Tendon and Knee Ligaments</i> , 19 J. Biomechanics, 425-432 (1986) (“Butler 1986”)
2029	Butler, et al., <i>Location-Dependent Variations in the Material Properties of the Anterior Cruciate Ligament</i> , 25 J. Biomechanics, 511-518 (1992) (“Butler 1992”)
2030	Ma, et al., <i>In vitro and in vivo mechanical properties of human ulnar and median nerves</i> , J Biomed Mater Res Part A 2013:101A:2718–2725 (“Ma”)

2031	Ni Annaidh, et al., <i>Characterization of the anisotropic mechanical properties of excised human skin</i> , J. Mech. Behavior of Biomedical Materials, 139-148 (2012) (“Ni”)
2032	Attorney’s Illustrated Medical Dictionary (1997) – “sheet”
2033	Dorland’s Illustrated Medical Dictionary (29th ed. 2000) – “sheet”
2034	Crisan, et al., <i>A Perivascular Origin for Mesenchymal Stem Cells in Multiple Human Organs</i> , Cell Stem Cell 3, 301-313 (2008)
2035	Lustig, et al., <i>Solute Diffusion in Swollen Membranes, IX. Scaling Laws for Solute Diffusion in Gels</i> , 36 J. Applied Polymer Science, 735-747 (1988)