

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

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

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
A.	Engagement.....	1
B.	Qualifications	1
C.	Materials Considered.....	5
II.	LEGAL STANDARDS.....	6
A.	<i>Inter Partes</i> Reviews.....	6
B.	Anticipation	7
C.	Obviousness.....	8
D.	Level of Ordinary Skill in the Art	10
III.	THE '223 PATENT.....	11
A.	Effective Filing Date	11
B.	Disclosure	11
C.	Challenged Claims	15
D.	Claim Construction	15
IV.	ANALYSIS OF ASSERTED GROUNDS	18
A.	Identification of Asserted Grounds	18
B.	Ground 1: Alleged Anticipation by Huang2	18
1.	Claim 1	18
a)	“... wherein a fast Fourier transform (FFT) analysis result of the fibers have adjacent major peaks with about 180° apart from each other.”	18
(1)	“major peaks”	18
(2)	“adjacent major peaks with about 180° apart from each other”	21
(a)	Lack of reliable testing.....	21
(i)	Dr. Simpson’s testing conflicts with Huang2	22
(ii)	Dr. Simpson’s testing protocol is not explained	28

b)	Dependent claims 2-12	32
2.	Claim 2	32
3.	Claim 3	36
4.	Claim 4	38
C.	Ground 2: Alleged Obviousness over Huang 2 and Kumbar	40
D.	Ground 3: Alleged Anticipation by Lee	43
1.	Claim 1	43
a)	“... wherein a fast Fourier transform (FFT) analysis result of the fibers have adjacent major peaks with about 180° apart from each other.”	43
(1)	“adjacent major peaks with about 180 apart from each other”	44
(a)	Lack of reliable testing	44
(i)	Dr. Simpson’s testing conflicts with the ’223 patent	45
(ii)	Dr. Simpson’s testing protocol is not explained	49
b)	Dependent claims 2-12	50
2.	Claim 2	50
3.	Claim 3	52
4.	Claim 4	53
5.	Claim 12	57
E.	Ground IV: Alleged Obviousness over Lee	58
V.	CONCLUSION	59
	APPENDIX A – MATERIALS CONSIDERED	62

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. (“Embodiy” or “Petitioner”) against claims 1-12 (the “Challenged Claims”) of U.S. Patent No. 10,137,223 (the “’223 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 '223 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 '223 patent “would be a Ph.D. student with a minimum of two years of experience in their faculty advisor’s

laboratory. At the relevant time, a [POSITA] would have understood the following technologies and techniques: electrospinning fibers, including for tissue engineering, tissue engineering techniques, and using/performing FFT analysis.”
Pet. 18.

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 ’223 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 ’223 patent.

III. THE ’223 PATENT

A. Effective Filing Date

41. In this proceeding, I apply March 14, 2013, the filing date of the provisional application that led to the application that issued as the ’223 patent, as the earliest effective filing date for this patent.

B. Disclosure

42. The ’223 patent describes a “scaffold comprising an aligned fiber.”
Ex. 1001, Abstract. The ’223 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 9:45–56, 15:61–65.

43. The '223 patent's scaffolds may be formed by electrospinning. *Id.* at 13:1–3. Electrospinning was known to generate very small diameter fibers, which the '223 patent describes as being “as small as one nanometer.” *Id.* at 2:17–19. The '223 patent states that its electrospun scaffolds may comprise collagen fibers. *Id.* at 13:27–46.

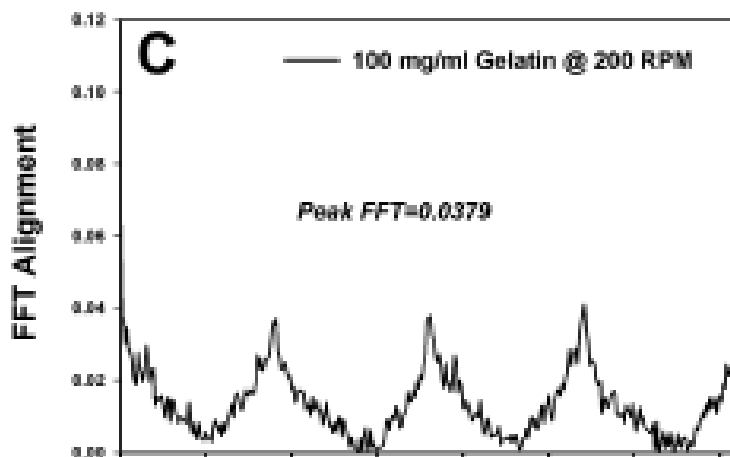
44. The '223 patent discloses embodiments where electrospun fibers are aligned in one direction. *Id.* at Abstract, 8:10–16.

45. To measure alignment of the scaffold's fibers, the '223 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 13:16–26.

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.

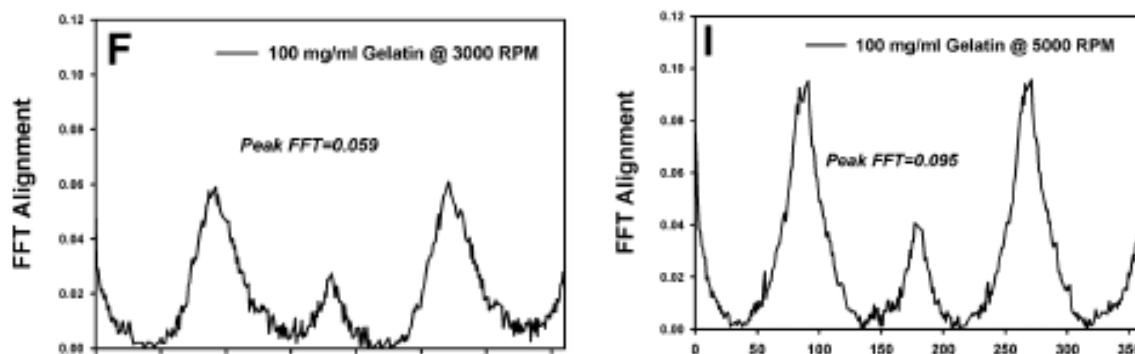
47. The 2008 paper explains that a FFT analysis result for “a random matrix will exhibit 4 peaks that occur every 90°. Peaks of nearly uniform height are a

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 '223 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 '223 patent, shown below. Ex. 1001, 13:3–7.

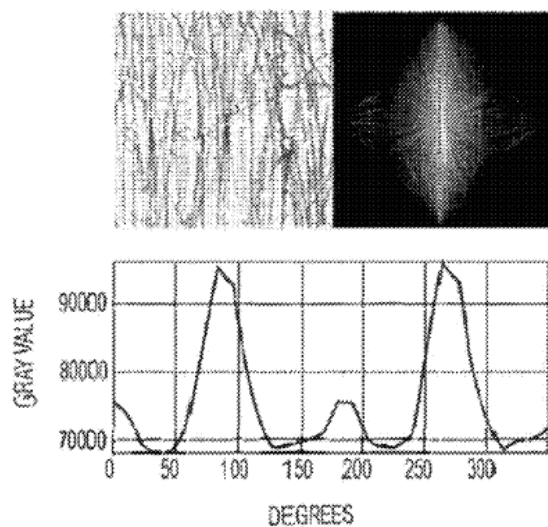


FIG. 8A

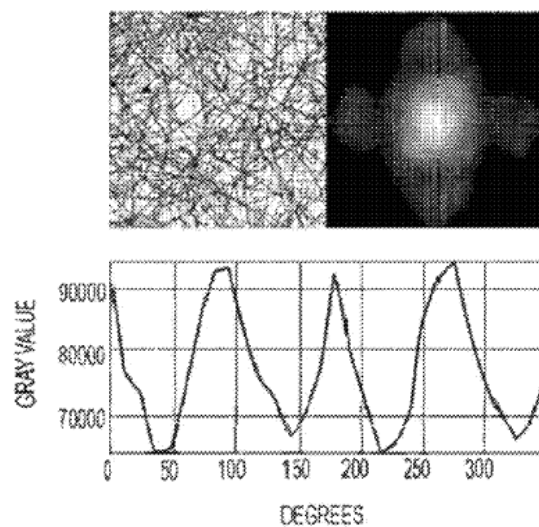


FIG. 8B

Id. at 13:24–26, Figs. 8A–8B.

51. The '223 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 1:56–57. As shown above, the FFT analysis result in the '223 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 13:24–26.

C. Challenged Claims

52. Claim 1 is the only challenged independent claim, and recites:

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

Ex. 1001, 23:6-9.

D. Claim Construction

53. 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.

54. Independent claim 1 recites: “a fast Fourier transform (FFT) analysis result of the fibers have adjacent major peaks with about 180° apart from each other.” Ex. 1001, 23:6–9. A POSITA would understand the definition and meaning of the term “major peaks” is provided in the '223 patent itself: “[t]he ‘major peaks’ herein

refer to peaks higher than the average of the peaks in the result.” *Id.* at 13:6–7.

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

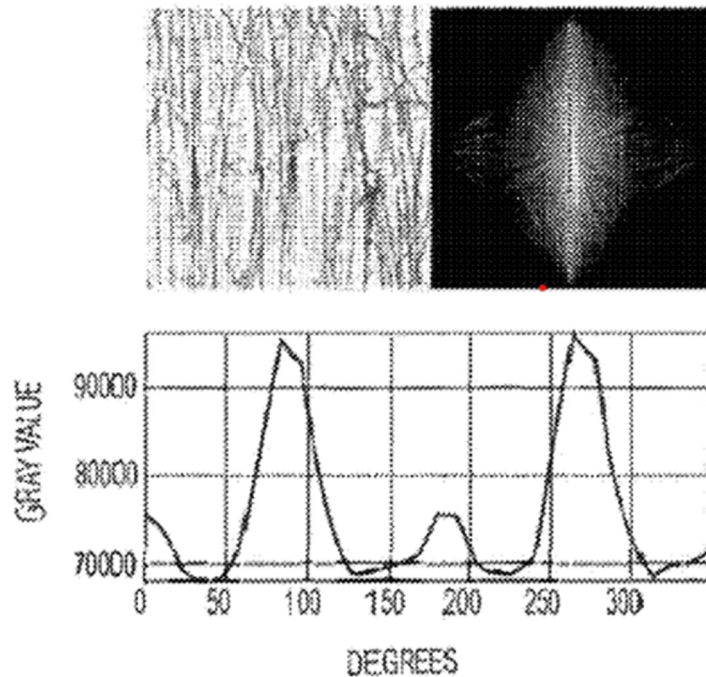


FIG. 8A

56. Based on the description in the '223 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.

57. 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.

58. 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.

59. In light of the '223 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

60. I understand that Petitioner identifies the following challenges (Pet. 5):

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

B. Ground 1: Alleged Anticipation by Huang2

61. In my opinion, Huang2 does not anticipate claims 1-12.

1. Claim 1

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

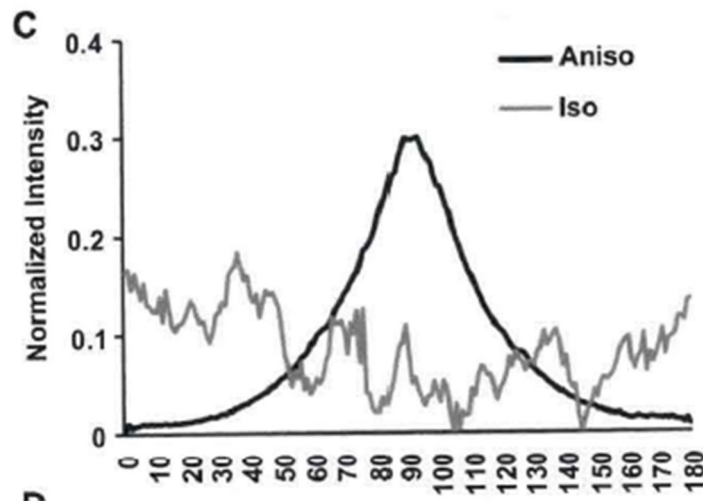
62. In my opinion, Huang2 does not disclose two aspects of this claim: “major peaks” and a FFT analysis result having “adjacent major peaks with about 180° apart from each other.”

(1) “major peaks”

63. 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.

64. 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.

65. 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.

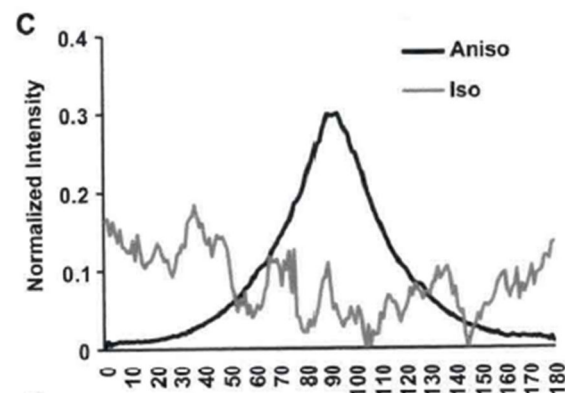
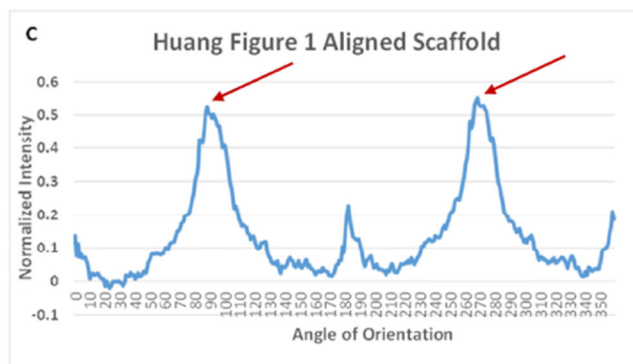
66. To determine the “average [height] of the peaks in the result,” a POSITA would sum the heights of all peaks in the FFT result and divide by the number of peaks (this approach would be the same even if the FFT result were extended to 360°). With a single peak reported by Huang2, and no smaller “minor”

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.

67. 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.

68. 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.

69. 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 ¶ 110, with Ex. 1005, Fig. 1C.



70. 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.a.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.

71. 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.a.2.

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

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

73. 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

74. 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 '223 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

75. Dr. Simpson states that his analysis is consistent with "the FFT analysis described in Huang2 and the '223 patent." Ex. 1003 ¶ 110. I disagree.

76. Unlike the FFT analysis in Huang2 or incorporated in the '223 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.

77. 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 '223 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.

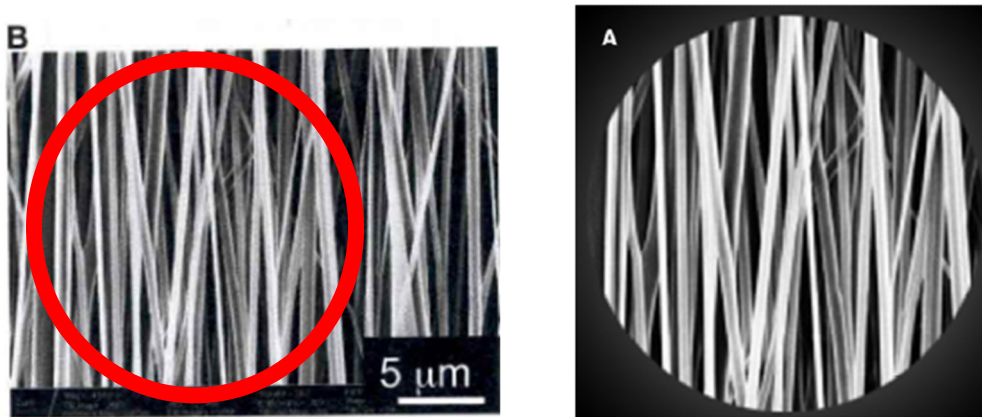
78. A POSITA would not find a reproduced or photocopied image to be suitable for FFT analysis. In fact, I have never performed FFT testing with a reproduced or photocopied image. Reproductions introduce noise, blur, and/or uneven illumination. As a result, image contrast is reduced, and fine details—essential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

79. FFT analysis based on reproduced or photocopied images is too unreliable.

80. 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.

81. 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.” *Compare* Ex. 1005, 1793, *with* Ex. 1003 ¶ 110.

82. 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.



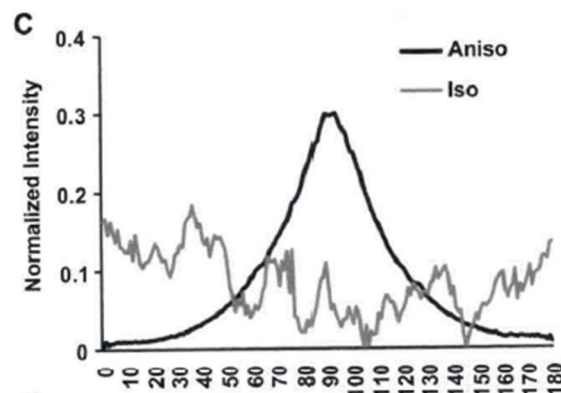
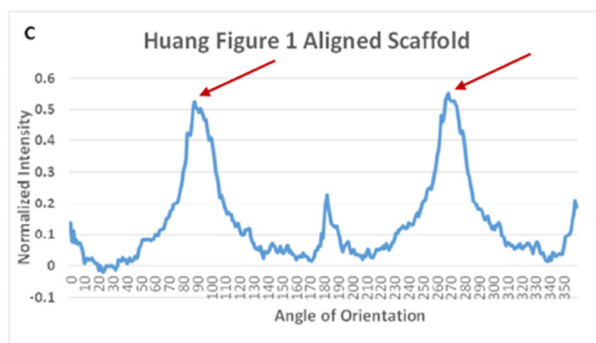
83. I agree with Dr. Simpson's past statements that a POSITA would recognize the importance of testing as much surface area as possible. Ex. 1010, 606 ("[M]easurements of scaffold anisotropy should be averaged over as large an area as possible. Local variations in fiber alignment can bias the 2D FFT 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.

84. 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.").

85. 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.

86. In fact, the FFT result produced by Dr. Simpson's testing differs from the result reached in Huang2. *Compare* Ex. 1003 ¶ 110, *with* Ex. 1005, 1793. These results are reproduced below, side by side.



87. As shown above, Dr. Simpson’s testing produced a markedly different result than Huang2 (even putting aside that Dr. Simpson’s testing is plotted to 360).

88. 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.

89. 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 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 (0.55 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.

90. Third, as discussed above, Huang2’s FFT lacks any minor peaks (*see supra* § IV.B.1.a.1), while Dr. Simpson’s FFT result depicts two smaller peaks at 0°

¹¹ Dr. Simpson did not explain the normalization protocol employed in his analysis. Absent such an understanding, a POSITA cannot account for the difference in 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.

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.

91. In sum, these FFT analyses convey fundamentally *different* results and, accordingly, fundamentally *different* information about the underlying fibers. 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.a.2.ii, a POSITA would be unable to interpret and reconcile his data.

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

92. 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.

93. 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.

94. 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.

95. 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.

96. 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 ¶¶ 110–111.

97. 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 ¶¶ 110–111.

98. 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 ¶¶ 110–111.

99. As discussed above, Dr. Simpson appears to have performed his testing based on a reproduction of the images depicted in Huang2. Ex. 1003 ¶¶ 110–111. 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 such as small-scale variations 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. 19 n.3)—provides sufficient illumination for testing and to what extent error may have been introduced. Ex. 1003 ¶¶ 110–111; Ex. 1005, 1 (cover page with library sticker). In my view, its resolution

is inadequate.

100. 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 ¶ 110 (caption, "Normalized intensity values"), Dr. Simpson does not state the extent or mechanism by which that was achieved and any error introduced. Ex. 1003 ¶¶ 110–111.

101. 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.

102. 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 ¶ 110. 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.

103. 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.

104. 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.

b) Dependent claims 2-12

105. Because claims 2-12 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 are anticipated by Huang2 at least because, as described above, Huang2 does not anticipate claim 1.

2. Claim 2

106. Claim 2 depends on claim 1 and recites that "the fibers comprise type I collagen in its native triple helical structure." Ex. 1001, 23:10-11. In my opinion, Huang2 does not anticipate this claim because it does not expressly disclose or necessarily possess this structure.

107. Huang2 does not expressly disclose that its fibers comprise type I collagen in its native triple helical structure. Huang2 states that it dissolved type I collagen and polycaprolactone ("PCL") in a 1,1,1,3,3,3-hexafluoro-2-propanol

(“HFIP”) solution for electrospinning, but does not specify the structure of the collagen that is present in the resulting electrospun fibers themselves, as the claim requires. Ex. 1005, 1792.

108. In my opinion, Huang2’s fibers do not necessarily possess collagen in its native triple helical form. It is not enough that Huang2 used type I collagen in its electrospinning process or did not use the term “gelatin.” Pet. 33; Ex. 1003 ¶ 117. A POSITA would have readily understood that many compounds cause type I collagen to denature out of its native triple helix structure. For example, collagen is denatured out of its triple helical structure by low pH levels caused by the breakdown of various polymers, like PCL; by exposure to various solvents, like HFIP; and by the activity of various enzymes used for cell culture, like those present in fetal bovine serum.

109. Given Huang2’s disclosure, a POSITA would have understood that its electrospun fibers necessarily present collagen that has denatured out of its native triple helix form, at least due to Huang2’s use of PCL and HFIP in preparing its electrospun scaffold, and fetal bovine serum in its cell culture process.

110. Huang2 utilizes PCL as a polymer that is blended with collagen. Ex. 1005, 1792. Although PCL is typically hydrophobic and degrades slowly, blending PCL with collagen renders that PCL/collagen blend hydrophilic instead, which slightly accelerates PCL’s degradation. This hydrolytic degradation caused

by the blending of PCL with collagen releases acidic byproducts and decreases the pH of the resulting electrospun fibers during storage. In particular, the degradation of PCL produces 6-hydroxycaproic acid. Ex. 2018, 1224, Fig. 5 (depicting the “degradation of PCL via hydrolysis” with 6-hydroxycaproic acid). The production of 6-hydroxycaproic acid necessarily degrades collagen by disrupting the hydrogen bonds and the other noncovalent interactions that otherwise maintain collagen in its native triple helical structure.

111. Huang² also utilizes fetal bovine serum in its cell culture process. Ex. 1005, 1792. A POSITA would have understood that fetal bovine serum also contains several hydrolytic enzymes including esterases that also degrade PCL. When pH decreases through the degradation of PCL, the native triple helix structure of the collagen blend unfolds.

112. Additionally, HFIP is used in Huang²’s electrospinning solution and also degrades collagen out of its triple helical form. Ex. 1005, 1792. I disagree with Dr. Simpson’s opinion that HFIP was known to stabilize collagen’s triple helix structure. Ex. 1003 ¶ 117. In my opinion, the exact opposite is true. A POSITA at the time of invention would have known that HFIP *denatures* collagen out of its native triple helix. Specifically, HFIP engages in hydrophobic and hydrophilic interactions, which unfold the triple helix by interfering with the hydrogen bonds that maintain collagen in its native triple helical structure. As these hydrogen bonds

are disrupted, collagen denatures into an “open-helical” form. This is a known drawback to use of HFIP as an electrospinning solvent. This structural change, involving the breaking of hydrogen bonds, leads to the loss of collagen’s triple helical structure and its unique properties.

113. This is confirmed by contemporaneous publications. For example, a 2008 study performed by Zeugolis et al. reported great losses of triple helical collagen when electrospun from fluoroalcohols like HFIP and concluded that these solvents denature collagen out of its triple helical form. Ex. 2019, 2294 (“[E]lectrospinning of collagen or co-spinning of collagen-synthetic polymers out of fluoroalcohols results in the creation of gelatin, a protein derived from denatured collagen and is characterized by destroyed a-chains, disrupted triple-helical and fibrillar structure and lacking internal structure or configurational order.”), 2308 (“Electro-spinning of collagen out of fluoroalcohols denatures collagen to gelatin.”). Because of this denaturation with HFIP, Zeugolis et al. explained that “the very properties that have established collagen as the leading natural biomaterial are lost when it is electrospun into nanofibres out of fluoroalcohols such as [HFIP].” *Id.* at Abstract (“We further identify the use of fluoroalcohols as the major culprit in the process.”), 2303 (“[E]lectro-spinning of collagen out of fluoroalcohols effectively denatures this biopolymer, and thus appears to defeat its purpose, namely to create biomimetic scaffolds emulating the collagen structure and function of the

extracellular matrix.”).

114. Collagen’s native triple helical structure is responsible for the beneficial mechanical properties of collagen. Loss of the triple helical structure will make the fibers and scaffolds much weaker.

115. Given that Huang2 “dissolve[s] PCL and collagen in HFIP” before electrospinning, Ex. 1005, 1792, and due to the well-known denaturing effect of PCL and HFIP, it is my opinion that the type I collagen used in Huang2’s electrospinning solution would have denatured such that Huang2’s resulting fibers would not necessarily comprise collagen in its native triple helical structure.

3. Claim 3

116. Claim 3 depends on claim 1 and recites that “the fiber has less than about 8 wt % residual calcium.” Ex. 1001, 23:12-13. In my opinion, Huang2 does not anticipate this claim.

117. Huang2 does not expressly disclose that its fibers comprise less than 8 wt % residual calcium. Huang2 is silent regarding the level of residual calcium. Huang2 also does not disclose the detailed experimental protocol for the isolation of collagen (collagen type I was purchased from Elastin Products Inc., Ex. 1005, 1792), which may have involved the use of calcium salts or calcium-containing reagents.

118. In my opinion, Huang2’s fibers do not necessarily possess less than about 8 wt % residual calcium simply because Huang2 did not use calcium in the

production of its fibers. Ex. 1003 ¶ 121; Pet. 34. A POSITA would have readily understood that residual calcium is necessarily imparted to electrospun fibers from a variety of conventional sources, including compounds utilized in both electrospinning and cell culture. For example, residual calcium levels are driven by the source of collagen and the presence of chemical cross-linkers, buffer solutions, or cell culture compounds.

119. As discussed regarding claim 2, Huang2 discloses that it utilizes fetal bovine serum (“FBS”) in its cell culture medium. Ex. 1005, 1792. A POSITA would have readily understood that FBS naturally contains high concentrations of calcium, which is necessary for growth of the cells seeded on the scaffold. When collagen scaffolds are placed in a cell culture medium with FBS, like Huang2’s, those scaffolds will chelate calcium present in the FBS. This will necessarily increase the fiber’s residual calcium level. This is especially so when carboxyl terminated PCL is present in the scaffold, like in Huang2. Carboxyl groups are part of the aspartic acid and glutamic acid amino acid residues in collagen, and they are located at one end of the PCL chains. When placed in the cell culture medium containing FBS because the carboxyl is deprotonated at physiologic pH (exists as COO-) and, therefore, is negatively charged. That negative charge will chelate positively charged calcium.

120. Accordingly, it is my opinion that a POSITA would have known that

Huang2's fibers necessarily include residual calcium and would not necessarily have less than 8 wt % residual calcium due to the use of these compounds when preparing Huang2's scaffold.

4. Claim 4

121. Claim 4 depends on claim 1 and recites that “the scaffold has an average porosity from about 60% to about 90%.” Ex. 1001, 23:14–15.

122. Huang2 states that electrospun scaffolds generally are “characterized” by “high porosity.” Ex. 1005, 1791 (“[E]lectrospun nanofibrous matrices characterized by ultrafine continuous nanoscale fibers, high surface-to-volume ratio, high porosity and variable pore-size distribution have great potential to mimic the skin ECM in both morphology and composition.”). But, Huang2 does not expressly disclose any porosity percentage, let alone one within the claimed range.

123. A POSITA would have understood that this description of “high porosity” is generally applicable to electrospun scaffolds having a *random* fiber arrangement; it was well known and understood that *aligned* electrospun fibers necessarily possess relatively lower porosity due to the fibers' alignment, e.g., their “closely packed aligned fibers.” See, e.g., Ex. 1018 ¶ 112. As compared to randomly arrayed fibers, aligned fibers pack together more tightly leaving smaller spaces between fibers and, therefore, lower porosity. To the extent the Petition relies upon Huang2's “aligned” embodiment, Pet. 29 (“highly aligned”), a POSITA would have

understood that this description of high porosity would not apply.

124. Additionally, the porosity of aligned electrospun fibers is influenced by many factors, including the electrospinning solution, the electrospinning process itself, fiber diameter, extent of alignment, density, and layering. *See, e.g.*, Ex. 1003 ¶ 32 (“The properties of the resulting fibrous scaffold depend on several factors, such as the polymer’s molecular weight, the solution composition, flow rate, charge, the distance between the syringe and the collector, and the motion and charge of the collector.”); Ex. 1006, 4-5 (explaining that an electrospun fiber’s “porosity and pore-size distribution greatly depend[] on the[] parameters selected for electrospinning”); *see also infra* § IV.C (incorporated by reference). Without knowing these factors, particularly the electrospinning solution composition, the porosity of a scaffold cannot be known without being specifically measured. A specific percentage is certainly not necessarily present.

125. It is my opinion that a POSITA would have understood Huang2’s reference to “high porosity” as inapplicable to aligned fibers and, moreover, as a relative term where the actual porosity would have been heavily dependent on various factors that are not evaluated in the Petition. It would not necessarily fall within the claimed range.

126. For reasons discussed further below, the Petition’s citation to the Kumbar reference does not alter my opinion, in part because Kumbar did not address

the porosity of aligned electrospun fibers comprising a PCL/collagen blend like Huang2, which will differ greatly from the porosity of Kumbar's non-aligned scaffold containing pure collagen. *See infra* § IV.C.

C. Ground 2: Alleged Obviousness over Huang 2 and Kumbar

127. In my opinion, Huang2 and Kumbar do not render obvious claim 4.

128. Claim 4 depends on claim 1 and recites that “the scaffold has an average porosity from about 60% to about 90%.” Ex. 1001, 23:14–15.

129. I disagree with Dr. Simpson's opinion that a POSITA “who desired to make aligned collagen blended fibers (as taught by Huang2) with ‘high porosity’ (as also taught by Huang2) would have been motivated to look at” Kumbar, which “teaches the desirability of high porosity and further discloses ranges of porosity within the scope of claim 4.” Ex. 1003 ¶ 169.

130. Porosity reflects the percentage of void volume in a structure. A scaffold's porosity is primarily a product of fiber diameter and fiber density caused, in part, by fiber alignment and fiber packing. Larger diameter fibers tend to lead to larger pore sizes, while smaller diameter fibers tend to lead to smaller pore sizes. And, as discussed above regarding Ground 1, more highly aligned fibers lead to lower porosity than more randomly aligned fibers due to the tighter packing of fibers in an aligned scaffold. *See also* Ex. 1018 ¶ 112. In other words, tightly packed aligned fibers present less void space between the fibers, decreasing the structure's

porosity. Similarly, the packing of fibers also dictates the porosity of a scaffold with randomly aligned fibers. Larger diameter randomly aligned fibers lead to larger pore sizes.

131. A scaffold's porosity ultimately depends on various electrospinning parameters. Both features that dictate porosity—fiber diameter and fiber packing—are controlled through variable electrospinning parameters. This is confirmed by Kumbar itself, which explains that “porosity and pore-size distribution greatly depend on the[] parameters selected for electrospinning.” Ex. 1006, 3; *see also* Ex. 1003 ¶ 32. Accordingly, it is these parameters that control the porosity of Huang2's scaffold. Kumbar's porosities do not apply to Huang2 because Kumbar and Huang2 utilize fundamentally different electrospinning parameters, namely different polymers and electrospinning solutions. Accordingly, they produce scaffolds with fundamentally different porosity.

132. Huang2 teaches that its scaffold is made from a 3:1 blend of PCL and collagen which is electrospun to produce aligned fibers. Ex. 1005, 1792. By contrast, Kumbar's cited embodiments involve either pure collagen porosity or cross-linked pure collagen. Ex. 1006, 7 (disclosing 89% and 71% porosity, respectively). Additionally, for these embodiments, Kumbar does not describe aligned fibers. *Id.*

133. When used in electrospinning, a PCL/collagen blend like Huang2's

possesses very different solution properties, which directly impact scaffold porosity, as compared to a solution containing pure collagen, like Kumbar's.

134. Specifically, the presence of PCL in Huang2's PCL/collagen blend increases solution viscosity because of the chain entanglements formed by PCL. This increased viscosity necessarily produces more uniform fibers without beads. It also produces fibers with larger fiber diameter. *See, e.g.,* Ex. 1010, 618 (Dr. Simpson stating that "fiber diameter and pore dimension ... can be largely controlled by regulating the concentration of polymer (viscosity and degree of chain entanglements) present in the starting solution").

135. By contrast, a POSITA would have understood that Kumbar's pure collagen electrospinning solution has lower viscosity and, consequently, produces smaller diameter fibers than the blend disclosed by Huang2.

136. Kumbar itself explains that these differences in polymer composition are determinative of the resulting properties, such as porosity. Ex. 1006, 3 ("[P]orosity and pore-size distribution greatly depend on the[] parameters selected for electrospinning."), 4 (explaining that "polymer and polymer solution properties play a significant role in controlling" structural morphology).

137. Dr. Simpson also testifies that "[t]he properties of the resulting fibrous scaffold depend on several factors, such as the polymer's molecular weight, [and] the solution composition," where alterations to those factors "can significantly

change the properties of the scaffold.” Ex. 1003 ¶ 32.

138. These differences in solution composition of a PCL/collagen blend as compared to pure collagen have not been accounted for in the proposed combination with Kumbar even though those parameters will dictate the resulting porosity. Accordingly, a POSITA would not have expected success in modifying Huang2’s scaffold to possess the claimed porosity where Huang2’s disclosure does not support such a high porosity.

139. A POSITA also would have understood that Huang2’s porosity necessarily would have been lower than that disclosed by Kumbar due to the alignment of Huang2’s fibers, where the embodiments that Petitioner relies upon in Kumar are not disclosed to have aligned fibers. Pet. 45 (citing Ex. 1006, 7).

140. Because Kumbar and Huang2 discloses fibers created from fundamentally different electrospinning solutions, with different compositions and solution properties, a POSITA would not have had a reasonable expectation of success in modifying Huang2’s scaffold to include the claimed porosities.

D. Ground 3: Alleged Anticipation by Lee

141. In my opinion, Lee does not anticipate claims 1-12.

1. Claim 1

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

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

142. In my opinion, Lee does not anticipate this limitation.

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

144. 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. 47-53.

145. 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. 52-53. 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.

(a) Lack of reliable testing

146. 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 '223 patent. Additionally, as discussed above regarding Ground 1 (which is incorporated by references), 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 '223 patent

147. Dr. Simpson states that his analysis is consistent with “the FFT analysis described in the '223 patent.” Ex. 1003 ¶ 188. I disagree.

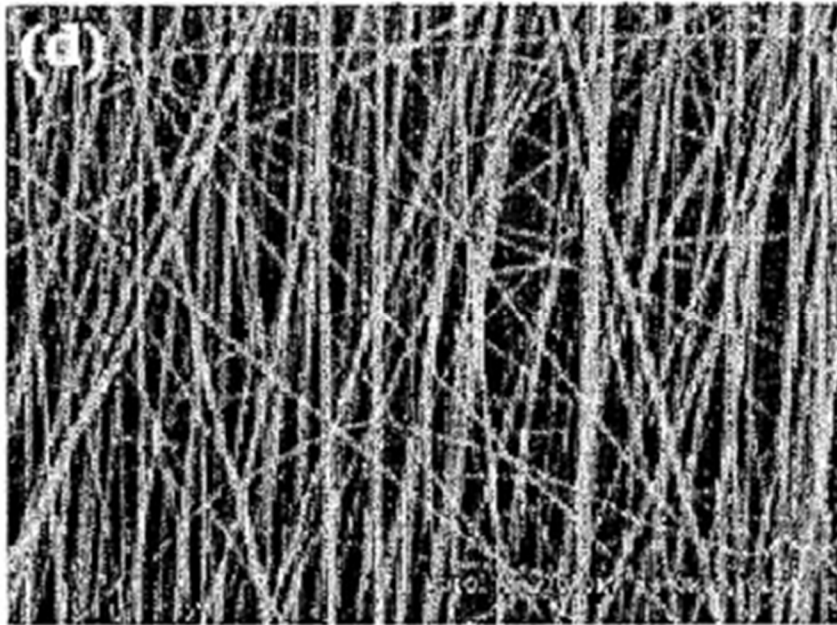
148. Unlike the FFT analysis in the '223 patent, Dr. Simpson performed his testing on a poor-quality photocopy of Lee fibers. Dr. Simpson did not test SEM images themselves as is customary and accepted in the field.

149. 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 '223 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.

150. 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.

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



Ex. 1003 ¶ 184. 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.

152. 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 ¶ 184 (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.

153. 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 '223 patent.

154. 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 ¶ 110, but he does not show or describe any such mask applied to Lee's image.

155. But Dr. Simpson testified during his deposition that he *did* in fact apply a mask to Lee's image. Ex. 2017, 162:4-10. This omitted information is essential. Without knowing where or how Dr. Simpson applied a mask, his FFT analysis cannot be evaluated. For example, it 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 '223 patent." Ex. 1003 ¶ 188. Specifically, the '223 patent incorporates the FFT analysis described in Dr. Simpson's 2008 paper (Ex. 1010), but this paper discloses only an *optional* mask—an option that was not exercised in the '223 patent. *See* Ex. 1001, Fig. 8A (depicting the tested image without a mask).

156. 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

157. 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.

158. As discussed above in my opinions 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.

159. 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.

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

161. 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 '223 patent. Absent that explanation, I am unable to sufficiently reproduce this test, further rendering it unreliable.

b) Dependent claims 2-12

Because claims 2-12 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 are anticipated by Lee at least because, as described above, Lee does not anticipate claim 1.

2. Claim 2

162. Claim 2 depends on claim 1 and recites that "the fibers comprise type I collagen in its native triple helical structure." Ex. 1001, 23:10-11. In my opinion, Lee does not anticipate this claim because it does not expressly disclose or necessarily possess this structure.

163. As described above regarding Huang2, which is incorporated herein by

reference, Lee is also silent regarding the structure of any collagen that is present in the resulting electrospun fibers themselves, as the claim requires. And, like above, Lee also dissolves type I collagen and PCL in HFIP for electrospinning and utilizes fetal bovine serum in cell culture. Ex. 1011 ¶¶ 63 (termed HFP in Lee), 69 (FBS).

164. In my opinion, Lee's fibers do not necessarily possess collagen in its native triple helical form because, as described above, a POSITA would have readily understood that collagen denatures out of its native triple helical structure due to many causes, including the presence of PCL, HFIP, and fetal bovine serum.

165. Given Lee's disclosure, a POSITA would have understood that its electrospun fibers necessarily present collagen that has denatured out of its native triple helical form. As described above, Lee's blending of PCL with collagen will slightly accelerate PCL's degradation. As it degrades, the acidic byproducts released will decrease the pH of the resulting electrospun fibers during storage, which will disrupt the hydrogen bonds and other noncovalent interactions that otherwise maintain collagen in its native triple helical structure. Ex. 2018, 1224, Fig. 5. Lee's use of fetal bovine serum will accelerate the degradation of PCL, as described above.

166. As also described above, a POSITA would have known that Lee's use of HFIP necessarily *denatures* collagen out of its native triple helix by interfering with the hydrogen bonds that maintain collagen in its native triple helical structure. *See* Ex. 2019, 2303 ("Electro-spinning collagen out of fluoroalcohols denatures

collagen to gelatin.”)

167. Given Lee’s use of PCL, HFIP, and fetal bovine serum, it is my opinion that the type I collagen used in Lee’s electrospinning solution would have denatured such that the resulting fibers would not necessarily comprise collagen in its native triple helical structure.

3. Claim 3

168. Claim 3 depends on claim 1 and recites that “the fiber has less than about 8 wt % residual calcium.” Ex. 1001, 23:12-13. In my opinion, Lee does not anticipate this claim.

169. Lee does not disclose the residual calcium content of its fibers, nor does it provide any characterization of it.

170. Lee also does not disclose the detailed experimental protocol for the isolation of collagen (collagen type I was purchased from Elastin Products Company, Ex. 1011 ¶ 62), which may have involved the use of calcium salts or calcium-containing reagents.

171. Moreover, as described above regarding Ground 1 and incorporated by reference, a POSITA would have readily understood that residual calcium is necessarily imparted to electrospun fibers from a variety of conventional sources, including the source of collagen and the presence of chemical cross-linkers, buffer solutions, or cell culture compounds.

172. Like with Huang2 above, Lee utilizes FBS in its cell culture medium. Ex. 1011 ¶ 69. A POSITA would have readily understood that FBS naturally contains high concentrations of calcium, which is necessary for growth of the cells seeded on the scaffold. When collagen scaffolds are placed in a cell culture medium like Lee's, those scaffolds will chelate calcium present in the FBS. This will necessarily increase the residual calcium level, especially when carboxyl terminated PCL is present because the carboxyl is deprotonated at physiologic pH and is negatively charged. That negative charge will chelate positively charged calcium.

173. Unlike Huang2 above, Lee's scaffold is also cross-linked with glutaraldehyde solution. Ex. 1011 ¶ 63. Glutaraldehyde is "implicated in the development of calcification." Ex. 2020, 1594. Glutaraldehyde-crosslinked collagen, like Lee's, mineralizes more effectively than un-crosslinked collagen because crosslinking enhances collagen's mechanical stability, which is crucial for mineralization and calcification. This contrasts with the claimed scaffold, which seeks to minimize calcium to less than 8 wt %.

174. It is my opinion that Lee's fibers necessarily include residual calcium and would not necessarily include less than 8% weight of residual calcium content.

4. Claim 4

175. Claim 4 depends on claim 1 and recites that "the scaffold has an average porosity from about 60% to about 90%." Ex. 1001, 23:14–15.

176. Lee discloses that some embodiments of electrospun scaffolds include “high porosity.” Ex. 1011 ¶ 55. Lee does not disclose that the exemplary scaffolds disclosed as its invention have high porosity, nor does Lee expressly disclose any porosity within the claimed range. To the extent the Petition relies upon Lee’s “aligned” embodiment, a POSITA would have understood that this description of high porosity would not apply.

177. As described above regarding Ground 1 and incorporated by reference, it was well known that aligned electrospun fibers necessarily possess a relatively low porosity due to the fibers’ alignment, e.g., their “closely packed aligned fibers.” *See, e.g.*, Ex. 1018 ¶ 112. As compared to randomly arrayed fibers, aligned fibers pack together more tightly leaving smaller spaces between fibers and, therefore, lower porosity. To the extent the Petition relies upon Lee’s “aligned” fibers, a POSITA would have understood that this description of high porosity would not apply.

178. Additionally, as described above, the porosity of aligned electrospun fibers is influenced by many factors, including electrospinning parameters. *See, e.g.*, Ex. 1006, 4-5 (explaining that an electrospun fiber’s “porosity and pore-size distribution greatly depend[] on the[] parameters selected for electrospinning”); Ex. 1003 ¶ 32. Without knowing these factors, particularly the electrospinning solution composition, the porosity of a scaffold cannot be known without being specifically measured. The Petition does not discuss the results of any such

measurement.

179. Additionally, the presence of PCL in Lee's PCL/collagen blend, Ex. 1001 ¶ 65, increases the electrospinning solution viscosity because of the chain entanglements formed by PCL. This increased viscosity necessarily produces more uniform fibers without beads. This also necessarily produces fibers with larger diameters. *See, e.g.*, Ex. 1010, 618 (Dr. Simpson stating that "fiber diameter and pore dimension ... can be largely controlled by regulating the concentration of polymer (viscosity and degree of chain entanglements) present in the starting solution").

180. It is my opinion that POSITA would have understood Lee's reference to "high porosity" as inapplicable to aligned fibers and, moreover, as a relative term where the actual porosity would have been heavily dependent on various factors. It would not necessarily fall within the claimed range.

181. In alleging this claim as anticipated, Petitioner mistakenly relies upon my issued patent to support its argument. Petitioner misreads my prior work, which does not support its anticipation argument. Pet. 56.

182. First, Petitioner turns to my prior patent because Lee discloses that, in some embodiments, the scaffold may be "shaped" using various methods such as "leaching," where a suspension of a porogen in a polymer solution is spread into a shape that resembles the final form and a solvent is used to dissolve away the

porogen, resulting in pore formation. Ex. 1011 ¶ 56. But the Petition does not propose modifying Lee by shaping so this disclosure is irrelevant.

183. Additionally in U.S. Patent No. 5,514,378 (“the ’378 patent”), my colleagues and I disclosed methods of preparing a porous biocompatible membrane to be used for tissue reconstruction of cartilage or bone. Ex. 1014, Abstract, 2:45–49. The teachings therein are not applicable to Lee for several reasons:

- The ’378 patent is directed to bone and cartilage implant. The appropriate porosity of those tissues varies greatly from that of the muscle tissue taught by Lee. The ’378 patent does not teach the fabrication of scaffolds conducive to the formation of myotubes or skeletal muscle.
- The ’378 patent teaches use of various polymers for its implants but does not employ collagen and/or collagen and PCL, as taught by Lee. *Id.* 3:7–10, 5:14–17. As discussed above regarding Kumbar, different polymers and polymer blends present different porosities.
- The ’378 patent teaches mechanisms to increase porosity that are not applicable to electrospinning. For example, the salt leaching technique disclosed in the ’378 patent allows an artisan to selectively and individually vary both porosity *and* pore size. But these features cannot be independently controlled through electrospinning, where, e.g., varying the fiber diameter impacts both porosity *and* pore size together.

184. In my opinion, a POSITA would not have looked to my earlier work to determine the porosity of a collagen-based electrospun scaffold like Lee's. The techniques disclosed in the '378 patent do not apply to scaffolds like Lee's and a POSITA would not have expected success in combining those teachings.

5. Claim 12

185. Claim 12 depends on claim 11, which depends on claim 1, and recites that the "cells are selected from the group consisting of stem cells ..." Ex. 1001, 24:24-27. Petitioner relies on Lee's disclosure that skeletal muscle cells, which are seeded on the scaffold, "may be provided by . . . differentiating *stem* or progenitor cell," and that myoblasts are "a type of muscle stem cell." Pet. 63-64 (citing Ex. 1011 ¶¶ 30, 40).

186. In my opinion, Lee does not anticipate this claim. Stem cells are a specific type of cell that is capable of self-replicating and differentiation. Ex. 2004 at 315 (defining stem cells as having "the capacity for both replication and differentiation, and has pluripotentiality"); Ex. 1001, 1:19–23 ("explaining that stem cells can differentiate "into osteoblasts, chondrocytes, ligament or tendon").

187. The skeletal muscle cells relied upon in the Petition, hSkMCs and myoblasts, are not stem cells because they are already differentiated into their specific cell type, i.e., muscle cells. Although these muscle cells might have been *derived* from stem cells, a POSITA would have understood that once they

differentiated into muscle cells, they were no longer stem cells.

188. Lee also speaks imprecisely in describing a myoblast as a “type of muscle stem cell.” In my opinion, a POSITA would understand, including from the remainder of Lee’s disclosure, that a myoblast is “capable of dividing and repopulating” to repair injured myofibers. In that way, a myoblast is similar to a stem cell in that it can self-replicate, as stem cells do. But hSkMCs and myoblasts, however, are *not* stem cells because they cannot differentiate into different cell types—the defining characteristic of a stem cell. Instead, they always remain as muscle cells and, with myoblasts being referred to as muscle progenitor cells. Although myoblasts may fuse with other myoblasts to form myotubes, that fusion does not produce a different cell type.

E. Ground IV: Alleged Obviousness over Lee

189. The Petition argues that Lee confirmed fiber alignment in several ways: through “scanning electron microscopy ... mechanical testing and also by calculating the angles of alignment for the fibers.” Pet. 65. The Petition also states that Lee’s images were analyzed with ImageTool 3.0 to determine fiber orientation. *Id.* at 66. The Petition argues that “there would have been motivation and a reasonable expectation of success for a [POSITA] to run an FFT on the aligned fibers fabricated in Lee.” *Id.* at 64. The Petition states this could have been done “to confirm the degree of alignment.” *Id.* at 65; *see also id.* at 50-53.

190. 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.

V. CONCLUSION

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

192. In signing this declaration, I recognize that it will be filed as evidence in IPR2025-00248 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.

193. 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. 10,137,223
9	Patent Owner’s Preliminary Response
14	Decision Granting Institution of <i>Inter Partes</i> Review

Exhibit Number	Description
1001	U.S. Patent No. 10,137,223 to Francis et al.
1002	’223 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) (“Huang2”) (available online Dec. 2, 2011)
1006	Kumbar et al., <i>Electrospun nanofiber scaffolds: engineering soft tissues</i> , Biomed. Mater. 3 (2008)
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)
1014	U.S. Pat. No. 5,514,378 to Mikos
1015	Jose et al, <i>Fabrication and Characterization of Aligned Nanofibrous PLGA/Collagen Blends as Bone Tissue Scaffolds</i> , 50 Polymer 3778-85 (2009)
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)
1017	Shoulders & Raines, <i>Collagen Structure and Stability</i> , 78 Annu. Rev. Biochem. 929 (2009)
1018	Kuo et al., U.S. Patent Application No. US 2011/0293685 A1, Pub. Date Dec. 1, 2011
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
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)