

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

**DECLARATION OF DAVID G. SIMPSON, PH.D.
IN SUPPORT OF REPLY TO PATENT-OWNER'S RESPONSE**

TABLE OF CONTENTS

	Page
I.	The Claims Do Not Require Arithmetically Averaging the Peaks.....2
II.	Huang2 Anticipates Claims 1-3 and 5-12.....10
A.	FFT Testing.....10
B.	Huang2 Anticipates Dependent Claims 2-3 and 5-12 23
III.	Huang2 and Kumbar Render Claim 4 Obvious 27
IV.	Lee Anticipates Claims 1-12.....30
A.	Claim 1 is Anticipated 30
1.	Lee’s Highly Aligned Fibers Have the Peaks Recited in Claim 1 30
2.	Dr. Mikos’s Criticisms of the FFT Testing of Lee in My Original Declaration Lack Merit 31
B.	Lee Anticipates Dependent Claims 2-12 34
V.	Lee Renders Claims 1-12 Obvious 35

I, David G. Simpson, Ph.D., declare as follows:

1. I am the same David G. Simpson that submitted a declaration, EX1003, in this case on December 4, 2024. I have provided my background, my technical documents, and my CV with that declaration.

2. The opinions contained in the Declaration are based on my professional experience and knowledge, as well as the documents that I reviewed in connection with my analysis.

3. My opinions are also based on my appreciation of how the person of ordinary skill in the art (“POSA”) would have understood the claims at issue and the specification of the ’223 patent as of March 14, 2013, which counsel asked me to assume as the relevant time period for my analysis. My opinions reflect how one of ordinary skill in the art would have understood the ’223 patent, Lee, Huang¹, Huang², and the state of the art as of March 14, 2013.

I. THE CLAIMS DO NOT REQUIRE ARITHMETICALLY AVERAGING THE PEAKS

4. Claim 1 requires “major adjacent peaks that are about 180° apart from each other.” (EX1001, cl. 1.) Dr. Mikos argues that a POSA would understand that term to require (1) selecting certain peaks; (2) identifying the heights of those peaks, (2) mathematically computing their arithmetic mean, (3) comparing the arithmetic mean to each of the peak heights, and finally (4) labeling the peaks that

are higher than the arithmetic mean as major peaks. (EX2015, ¶¶56-57.) I refer to this as Dr. Mikos's arithmetic mean test. Dr. Mikos bases his arithmetic mean test on one sentence in the patent, that "[t]he 'major peaks' herein refer to peaks higher than the average of the peaks in the result." (EX2015, ¶54 (citing (EX1001, 13:6-7).)

5. I disagree with Dr. Mikos's arithmetic mean test. Instead, it is my opinion that a POSA would have understood that the claims require a visual inspection.

6. It is my opinion, that identifying "major peaks" is a visual test that works by comparing the relative size of the peaks present and this is what is meant by examining whether peak heights are higher than an "average." This is the test that I used in my published papers, including the Ayres 2008 paper, which is incorporated into the text of the '223 patent.

7. In none of my papers, either Ayres 2006 or 2008, did we assign numerical values to the peaks for the purpose of calculating an arithmetic mean to determine major peaks and fiber alignment. Instead, we examined visually the peak or peaks to determine whether they demonstrated fiber alignment:

- "The 2D FFT alignment 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). 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.” (EX1010, 610).

- “The overall 2D FFT alignment value for a scaffold is determined by visually inspecting and selecting the maximal value from the peak of the alignment plot..” (*Id.*, 613.)
- “The principal axis of fiber alignment is determined by the position of the alignment peaks.” (*Id.*, 610.)
- “Note that peak shape and height in the 2D FFT alignment plot report the relative degree of alignment present while the peak position reports the principle axis of orientation for the fiber field.” (*Id.*, 608.)
- “As subjectively judged from SEM images, a representative FFT analysis of a ‘random’ matrix and an ‘aligned’ matrix are presented in Fig. 1.” (EX1013, 3.)
- “For this type of analysis, the degree of fiber alignment in a data image is reported by the height and shape of the peak generated by the FFT plot (Fig. 1). The higher the peak, the more precisely aligned the fibers are along a single axis of orientation.” (*Id.*, 6.)

8. We did not assign numerical values to peaks in Ayres 2008 to determine the major peaks in a given scaffold. For the purpose of comparing different scaffolds, we did calibrate the numerical values of peaks on the different scaffolds to normalize the results so that they were on the same scale. But this is completely different than Dr. Mikos's arithmetic mean test to determine major peaks.

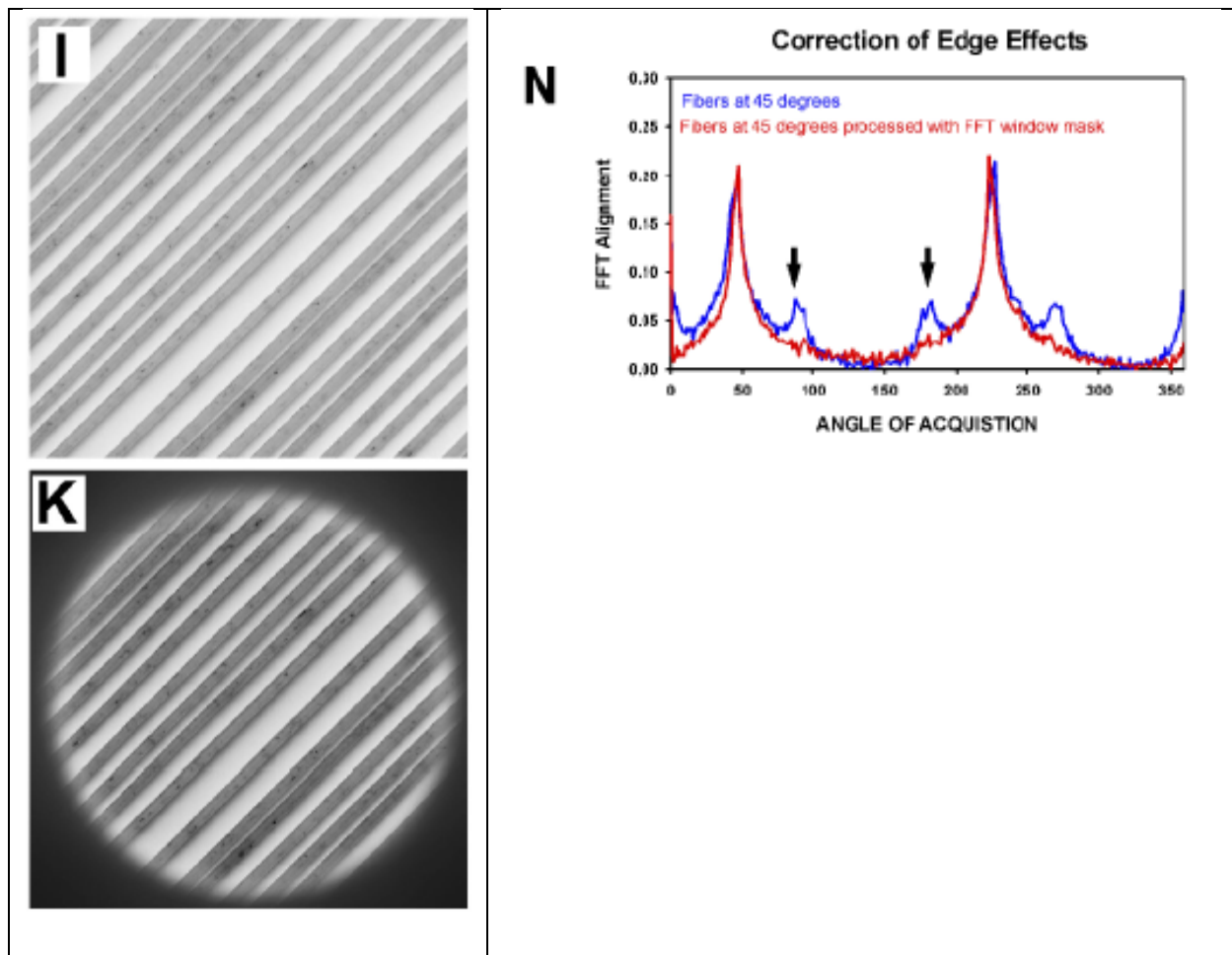
9. In fact, in my review of the prior art in this case, I have not seen any publications (including Huang1 and Huang2) that carry out Dr. Mikos's test to identify major peaks and fiber alignment. And Dr. Mikos testified that he has also not seen any prior art that uses his arithmetic mean test. (EX1220, 94:20-95:7)

10. There is also no evidence in the '223 patent itself that the inventors carried out Dr. Mikos's test. The patent does not identify any peak values, does not average the value of these peaks, and does not explain how the alignment peaks are above this average. (EX1001; *see also* EX1220, 64:6-17.) That analysis is just not in the '223 patent.

11. There are many problems Dr. Mikos's arithmetic mean test. Dr. Mikos's test appears to require the presence of what I consider noise or other imperfections in the FFT to satisfy his test. (EX1010, 615 ("The larger peaks report the principle axis of alignment while the smaller peaks correspond to background information, noise and edge effects (Fig. 3M).").)

12. While Dr. Mikos disagrees with my characterization of noise, he testified that his test does require some fibers that are *not* aligned, so there are more than two peaks. (EX1220, 79:2-13, 80:6-16.) I did not see any discussion in the '223 patent requiring the presence of non-aligned fibers to fall within the scope of the claim, and I do not believe a POSA would agree with this conclusion. I also believe that this requirement is inconsistent with my Ayres 2008 publication, which identified alignment plots with only two peaks as having major peaks showing alignment. (EX1010, 614 (Fig. 3N), 615.) In fact, as set forth in Ayres 2008, smaller peaks, in the FFT alignment plot of an aligned scaffold, generally correspond to “background noise” and/or “edge effects.” (*Id.*, 615; EX2017, 92:12-15, 118:13-119:5.)

13. For example, Ayres 2008 teaches a single *control* sample of highly aligned fibers arranged at a 45° angle, processed in two different ways into two different images, depicted in Figure 3, I and K. (EX1010, 614-15.) The FFT alignment plot for these images is shown in Figure 3, N. (*Id.*)



14. There is a red and a blue trace, and both traces measure the *same* fibers from the *same* scaffold and both show alignment. Even though the scaffolds underlying the blue and red FFT alignment plots are the same, the number of “peaks” in the alignment plots are different. (EX1220, 83:21-84:23.) The red trace has two peaks, while the blue trace has those two peaks, plus four extra small artifacts, which I explained in Ayres 2008 are most likely noise from edge effects. (EX1010, 614-15.) These artifacts are pointed out by arrows in the blue trace. (*Id.*, 614 (Fig. 3 description).) Ayres 2008 teaches that the red trace used a mask to

eliminate these edge effects. (*Id.*, 614-15.) Indeed, the red trace with *only* two peaks in the 360° field is the most accurate trace because it avoids the artifacts caused by edge effects and it doesn't otherwise markedly change the overall plot. (*Id.*, 615.) Nor did the mask change the position of the alignment.

15. But according to Dr. Mikos's test, the red trace (without the noise) that only contains two peaks would fall outside the scope of the claim, but the blue trace (with the noise) could fall within the scope of the claim according to his arithmetic mean test. (EX1220, 83:21-84:23.)

16. Dr. Mikos's construction makes no sense because both traces measure the same scaffold. Whether a scaffold is aligned or not is a property of the scaffold—and does not depend on how that scaffold is measured.

17. Huang2 is so highly aligned, like the red trace, that it would also only depict two major peaks if the field was extended to 360° and thus is aligned with two major peaks 180° apart, just as shown by Ayres 2008.

18. There is yet another problem with Dr. Mikos's test. The '223 patent only has two alignment plots, Figures 8A and 8B. Dr. Mikos states that, as indicated by the '223 patent, Figure 8A in the '223 patent shows aligned fibers but Figure 8B shows "random fibers." (EX2015, ¶51 (citing EX1001, 1:56-57).) But Dr. Mikos's arithmetic mean test shows that the *random* sample shown in Figure

8B does fall *within* the scope of claim 1. This undermines the arithmetic mean test's ability to determine alignment.

19. Figure 8B has peaks at 0 (value of 90,440), 90 (value of 93,630), 180 (value of 92,570) and 270 (value of 94,600). I obtained these values by measuring the y-axis using a precision micrometer to determine the scale between 80,000 to 90,000 and measuring the peak height from 80,000. To reiterate, the '223 patent did not measure the heights of the peaks in Figure 8B. (See EX1001.) Dr. Mikos essentially agrees with these numbers. (EX1220, 69:2-23; *see also id.*, 64:6-66:11.) The arithmetic mean of these four peaks is 92,810. Thus, there are two peaks above the “average” according to Dr. Mikos’ arithmetic mean test—the peaks at 90° (value of 93,630) and 270° (value of 94,600). These peaks are located 180° apart and thus, under Dr. Mikos’s test, the random sample would fall within the scope of the claim. But this is the *opposite* of what the specification teaches. In my opinion, this means that Dr. Mikos’s test cannot be the correct meaning of the claim. In contrast, under the visual test in Ayres 2008, which I believe is how a POSA would understand the claims, the random sample has “nearly uniform peak heights,” (EX1010, 609) so it does not meet the claims, as taught by the specification.

20. For all the above reasons, it is my opinion that Dr. Mikos’s arithmetic mean test as the definition for “major peaks” is not correct. And if it is correct, that

would mean claim 1 encompasses the random fibers in Figure 8b, which is the opposite of what Dr. Mikos and the specification teach.

II. HUANG2 ANTICIPTES CLAIMS 1-3 AND 5-12.

A. FFT Testing

21. In my earlier declaration, I tested the image of the fibers set forth in Huang2 and found that it has the requisite two peaks required by the claims of the '223 patent. (EX1003, ¶¶110-11.)

22. The plot from my earlier declaration is below. (*Id.*, ¶110.)

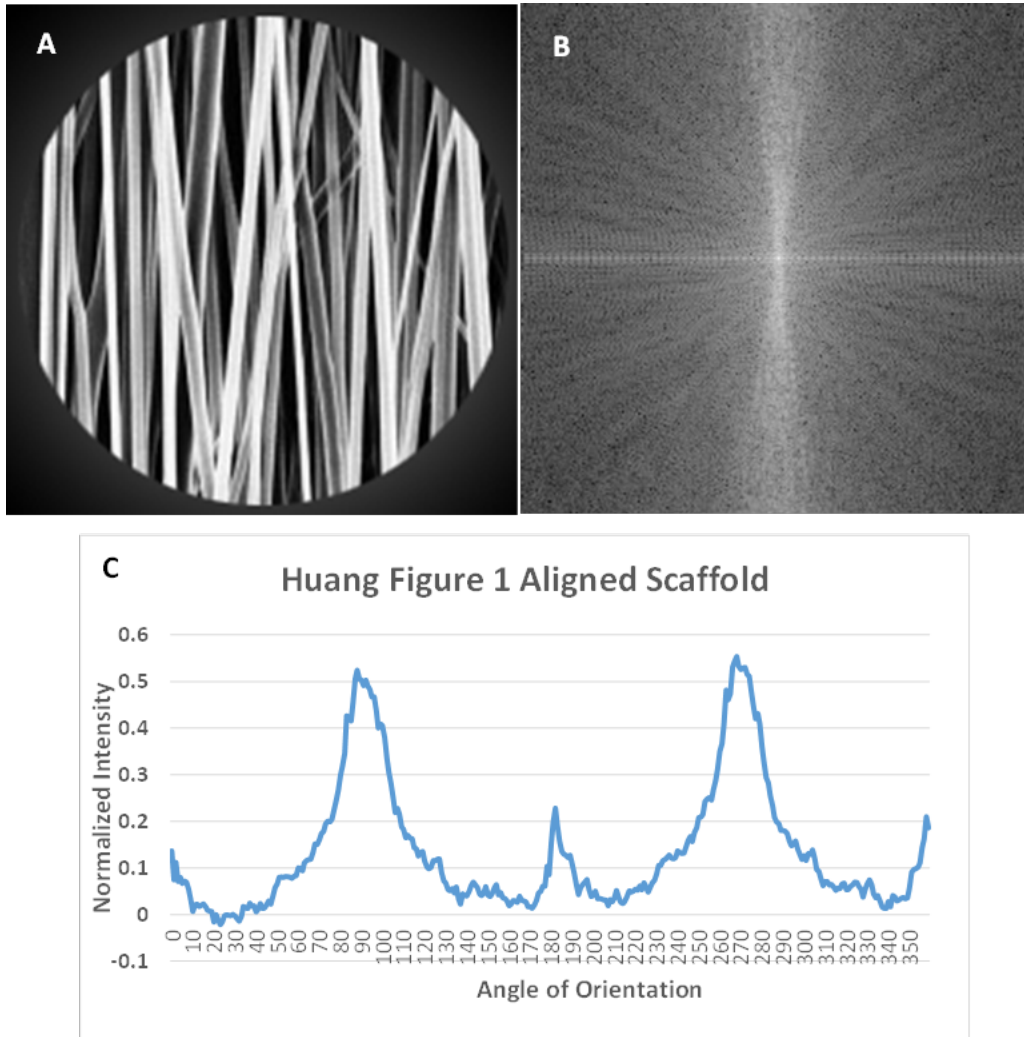


Figure 2. (A) Figure 1 from Huang aligned scaffold cropped and masked for 2DFFT. (B) 2DFFT spectrum of aligned scaffold, the image has been rotated to correct for the rotation intrinsic to the FFT analysis. (c) Normalized intensity values for aligned scaffold 0-360 degrees.

23. Under the correct visual test, there are two peaks separated by 180 degrees (the peaks at 90 and 270) that define the axis of alignment. It is my opinion that the “peaks” at 0° and 180° constitute artifacts, such as background noise.

24. Dr. Mikos argues that a POSA would not credit the testing in my original declaration because it is not scientifically valid. (EX2015, ¶¶74-104.) I disagree. Initially, I note that Dr. Mikos has never performed the Ayres 2008 technique in any of his published papers. I understand from Dr. Mikos's deposition that he has only used FFT to measure the alignment of electrospun fibers in one published paper. (See EX1220, 32:8-20, 35:2-36:17, 50:8-20). I have examined that paper, EX1203, and it does not perform the method in Ayres 2008 that is incorporated into the '223 patent. Indeed, it does not contain an FFT alignment plot. Dr. Mikos testified that Lee did not do the Ayres 2008 testing, and he testified that EX1203 conducted the same type of analysis as Lee. (EX1220, 189:12-191:7.)

25. I also note that, Dr. Mikos states that he "generally agrees" with my definition of a POSA, but he appears to add additional requirements to the POSA definition. (EX2015, ¶¶38-39.) To the extent that Dr. Mikos is saying that a POSA would need to have earned a Ph.D., (*id.*), I disagree. The first author of Ayres 2006 and Ayres 2008 papers was a graduate student. I further disagree with Dr. Mikos to the extent that he is trying to limit the field to engineering. For example, I have a Ph.D. in cellular, molecular, and structural biology, and I am the senior author of the Ayres paper. Therefore, Dr. Mikos's definition is too limiting and would in fact exclude the authors of the Ayres 2008 paper that was incorporated into the patent.

26. Dr. Mikos also does not show how any of the alleged problems with the analysis would actually make a difference to the testing results. In fact, Dr. Mikos does no testing of his own showing how his criticisms would actually affect the results.

27. Dr. Mikos specifically criticizes my placement of the circular projection for the FFT analysis (EX2015, ¶94), the image type used in my analysis (*id.*, ¶96), illumination (*id.*, ¶97), noise (*id.*, ¶98), software version (*id.*, ¶160), normalization (*id.*, ¶101), and masking (*id.*, ¶102).

28. I performed my analysis according to Ayres 2008, which is the level of detail provided in the '223 patent. (EX1001, 13:16-26.) Dr. Mikos acknowledges that none of the details he pointed to are spelled out in the '223 patent. (EX1220, 116:2-12, 117:10-16, 118:1-10.) A POSA would plainly know how to carry out the Ayres 2008 method, and would follow the same method that I used.

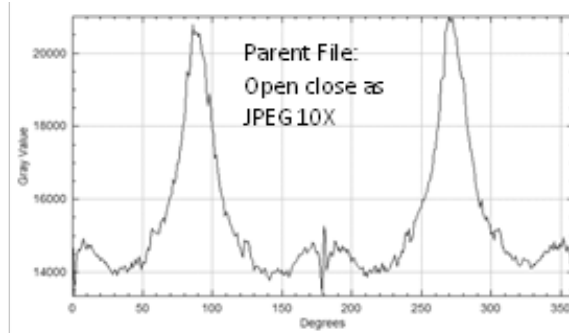
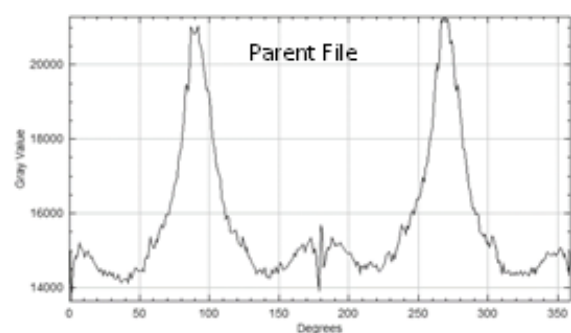
29. Regarding the placement of the circular projection for the FFT analysis (EX2015, ¶94), I used the largest circle tangent to the edges of the image (EX2017, 165:9-11), as exactly described in Huang2 (EX1005, 1792) and Ayres 2008 (EX1010, 608 (Figure 1B), 609).

30. Regarding the image type (EX2015, ¶96), the only reason to use a specific image is to preserve image quality (EX1010, 607). I testified that the

image from Huang2 was more than sufficient, that FFT is a “pretty forgiving” technique, that even an “imperfect image can be used,” and that Biomaterials would not have published Huang2 without an adequate image. (EX2017, 61:11-15, 138:23-139:14, 142:10-18.) In my judgment, the image published in Biomaterials was of more than adequate quality to conduct a valid FFT analysis on. Indeed, in Ayres 2006, the pictures were originally taken on film and then scanned into a computer before analysis, demonstrating that the FFT does not need to be run on an original image. (EX1013, 3 (“images were captured on Polaroid film, digitized via a flatbed scanner”), 4 (FFT analysis used “digitized SEM images”).) The scanner definitionally could not scan the image at the same resolution as the original analog picture.

31. Additionally, Ayres 2008 teaches that uncompressed .TIF files are preferred because “the image compression used in .JPG format will degrade image integrity” when repeatedly saved over. (EX1010, 607.) That means that if you open a JPEG, save it again, and then close it, the image may be altered. After a large number of times saving over the original image, the image will degrade. But if you open a .TIF, save it, and then close it, the image will not degrade, making .TIF preferred over JPEG for archiving data. In my analysis, I did not open and close the image from Huang2 multiple times.

32. I have also conducted additional testing to show that JPEG files do not meaningfully degrade an image for FFT testing if opened and closed a reasonable number of times. To do this, I took the image from Huang2 and made an FFT alignment plot, following the Ayres 2008 method. As discussed below, for these FFT plots I did not use a mask, to show that the use of a mask in my original testing did not affect whether the plot shows two major peaks and thus alignment. That image is on the left below. Then, I took the image from Huang2 and saved it as a JPEG. I then opened that JPEG and saved it again under a new filename, closed it, reopened the newly saved file, and repeated this open–save–close process ten times, each time saving over the immediately prior image. After ten successive save cycles, I generated an FFT alignment plot without a mask, following the Ayres 2008 method. That image is on the right. Both FFT alignment plots show two major peaks.



33. I further note that JPEGs can compress files even more than PDFs, meaning that a PDF has less degradation than a JPEG.

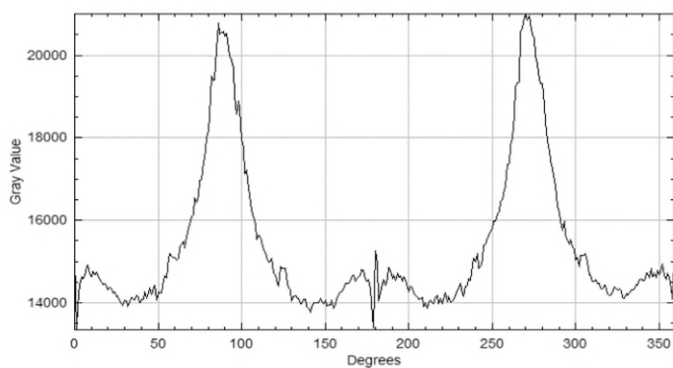
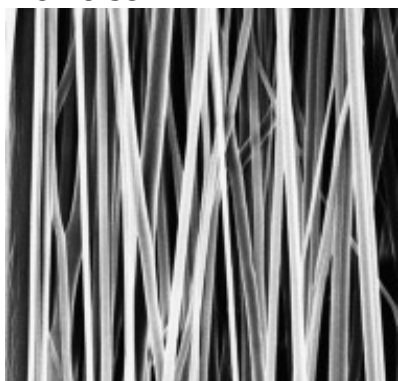
<https://www.adobe.com/creativecloud/file-types/image/comparison/jpeg-vs-pdf.html> (“PDFs will often be higher quality than JPEGs. This is because JPEGs compress images, leading to a loss in quality that you can’t regain. Visuals saved as PDF are of very high quality and even customizable, making them the file format of choice for printers.”)

34. Regarding illumination (EX2015, ¶97), at my deposition, I explained that Biomaterials is a high-quality journal and would be reluctant to publish images if they are not adequately illuminated. (EX2017, 142:10-18.) The image in a Huang2 publication has all the hallmarks of an evenly illuminated image of fibers—neither side is brighter than the other. Additionally, uneven sample illumination will result in an FFT alignment plot that does not align with the x-axis. That means if you draw a straight line through the low points between the peaks, that line would significantly tilt instead of running parallel to the x-axis. (EX1010, 612.) That is not the case with the Huang2 FFT, which is parallel to the x-axis. Moreover, the dynamic range is more than adequate for an FFT as well—some pixels are entirely black, and some pixels are entirely white.

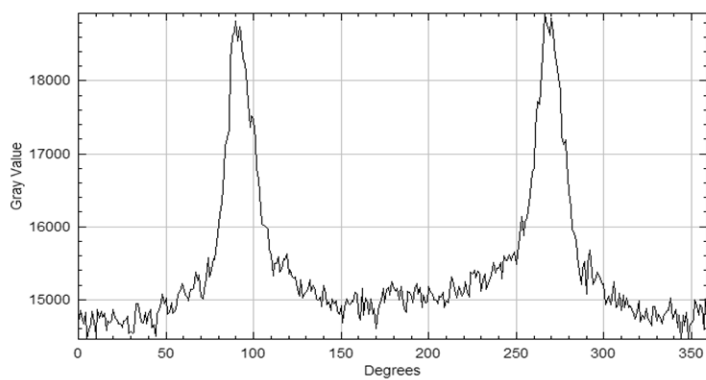
35. Regarding noise (EX2015, ¶98), it is my opinion that the image I downloaded for Hunag2 is very clear and does not possess “noise” that would preclude me from running a scientifically valid FFT. In addition, I have now run additional tests to show the effects of noise. To do this, I sequentially added salt

and pepper noise, which adds random black and white pixels, to Huang2's image using ImageJ's noise filter and then created FFT alignment plots of the increasingly noisy images. The results are below. They make clear that noise, even large amounts, does not impact whether the FFT can detect alignment—i.e., two major peaks. Nor does it alter the position of the peaks.

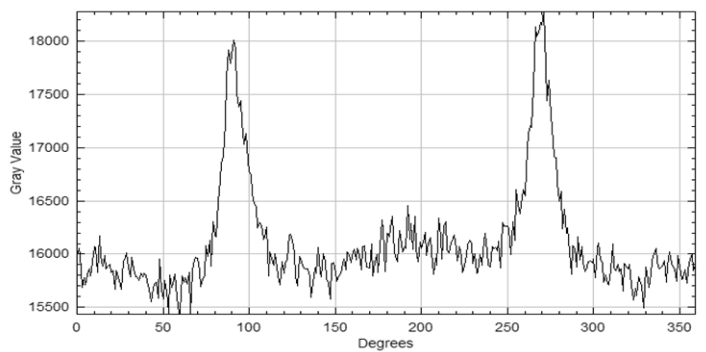
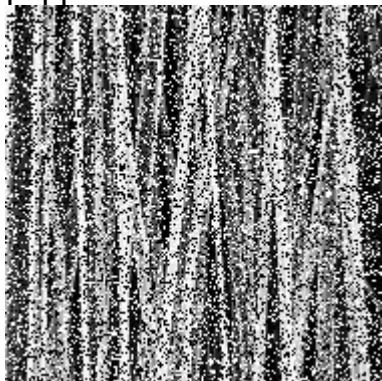
No noise

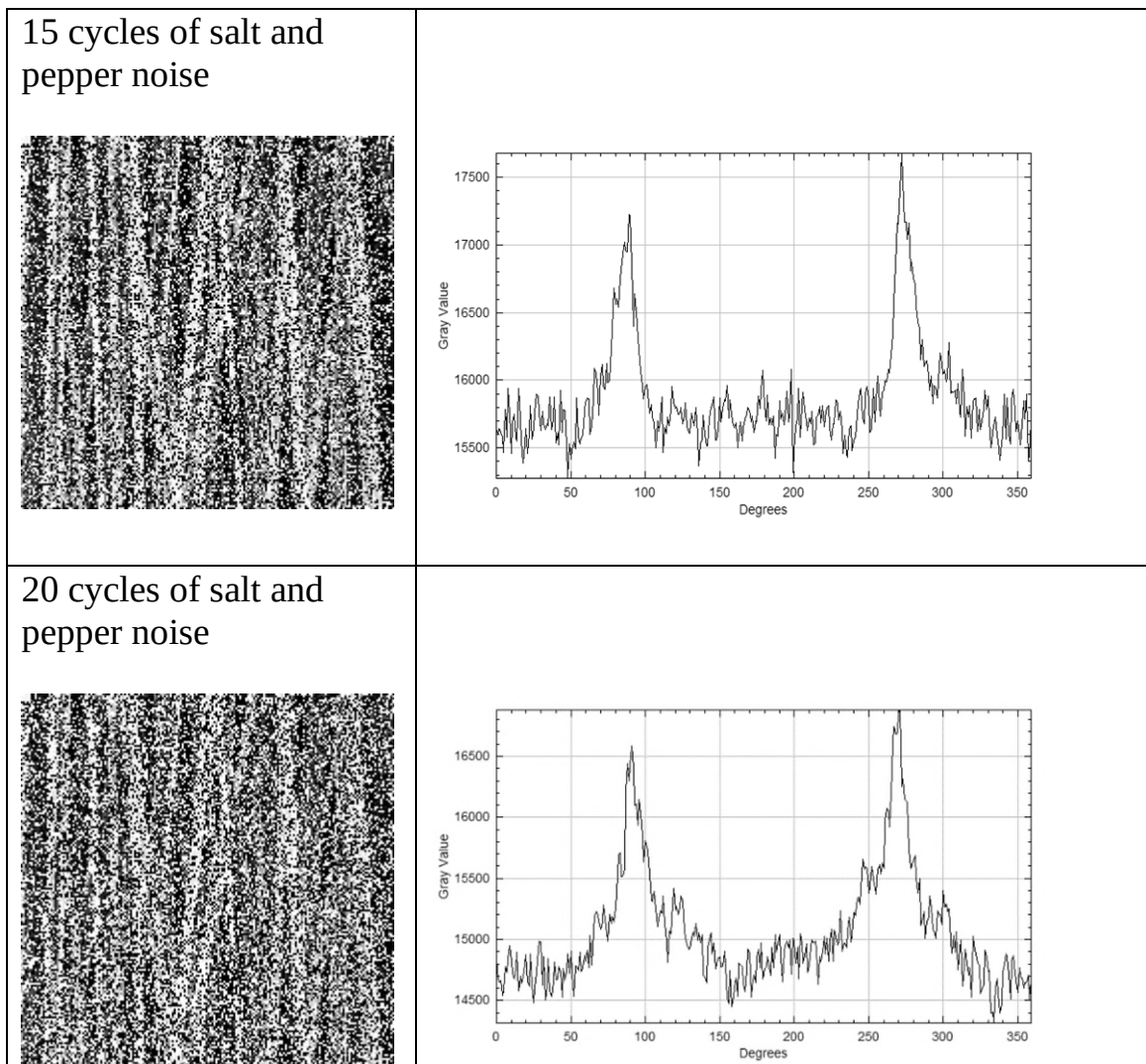


2 cycles of salt and pepper noise



10 cycles of salt and pepper noise





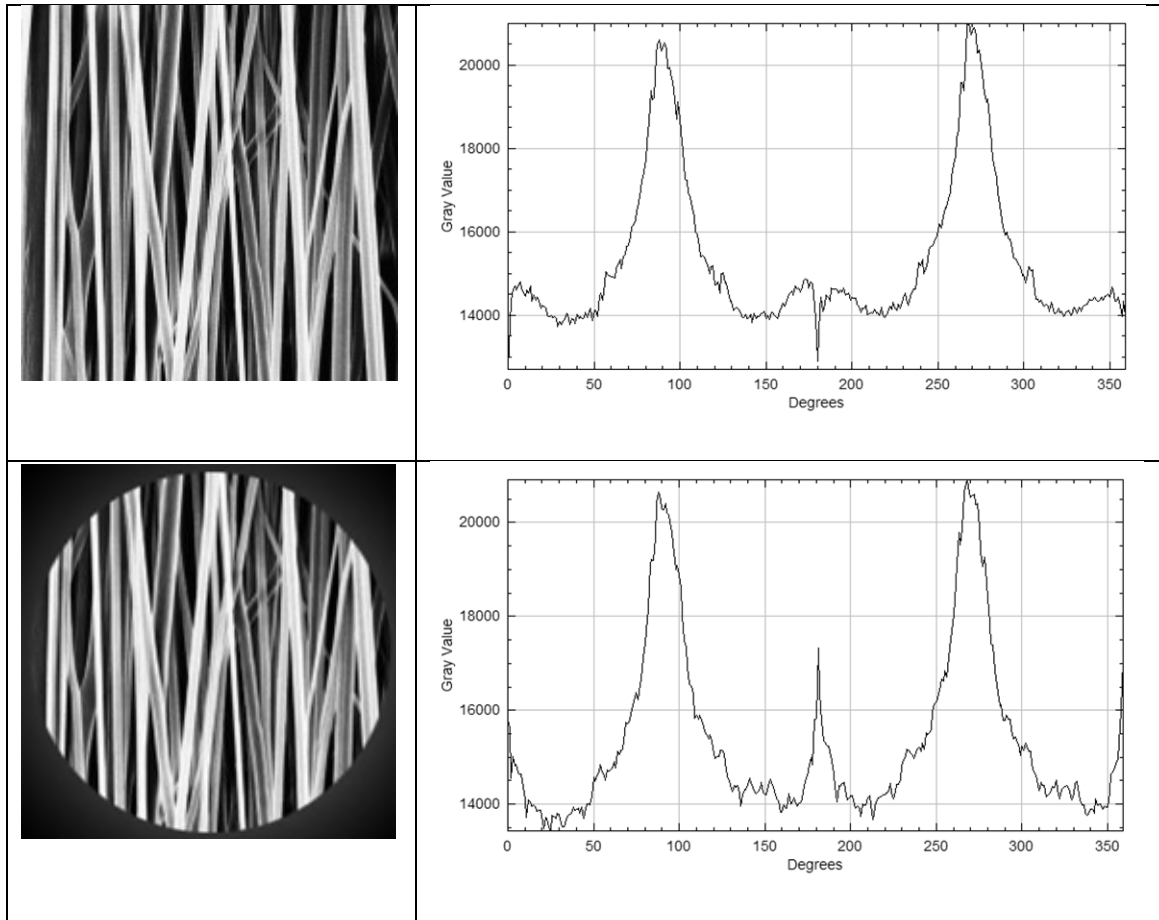
36. Regarding software version (EX2015, ¶160), it not important to know the version (EX2017, 161:16-21), I used the most recent version, and that all that matters is that the version had been corrected in line with Ayres 2008 (*id.*, 141:10-19). Some early versions of the program used unit circle with the 0 in a nonstandard position, which is easily remedied by rotating the image or changing the unit circle. A POSA would readily recognize and address the nonstandard unit

circle. In fact, Ayres 2008 does not even list its software version, and neither does the '223 patent. (See EX1010, 607; EX1001.)

37. Regarding normalization (EX2015, ¶101), normalization would not affect the number or location of the major peaks. Normalization is done to calibrate different alignment plots taken from different scaffolds so they can be compared on the same scale.

38. Regarding masking (*id.*, ¶102), Ayres 2008 discloses the use of an optional mask. (EX1010, 615.) The goal of a mask is to reduce noise. (*Id.* (“Processing the image with a window mask removes this spurious information without altering the height of the alignment peaks.”).) Using the mask as I did in my original analysis is perfectly consistent with Ayres 2008, and thus the '223 patent, whose only discussion of FFT analysis is incorporating Ayres 2008 by reference. (EX1001, 13:16-26.) The use of a mask does not change the position of the alignment peaks.

39. Regardless, I performed additional testing on Huang2 with and without a mask—and both show the requisite peaks. The results are below. They both show two major peaks separated by 180 degrees. The only difference in the alignment plots concerns the artifacts or noise peaks. Like the differences noted in Ayres 2008, Figure 3, discussed above, where there were differences in artifact peaks between the FFT of masked and unmasked samples.



40. Dr. Mikos further argues that my testing should be disregarded because it is different from the FFT alignment plot in Huang2. (EX2015, ¶¶86-91.) Initially, as stated in my original declaration, a POSA would understand that the one peak described in Huang2 from 0 to 180 would have a symmetrical peak from 180 to 360, and indeed I demonstrated that in my testing. (EX1003, ¶¶110-11.) Dr. Mikos points to the lack of minor “peaks” in Huang2. (EX2015, ¶90.) But, as set forth in Ayres 2008, smaller peaks, like the ones in the FFT alignment plot in my original declaration (EX1003, ¶110), correspond to “background noise.” (EX1010,

615; EX2017, 92:12-15, 118:13-119:5.) Regardless of Dr. Mikos's reliance on background noise, both the FFT alignment plot in my original declaration (EX1003, ¶110) and the FFT alignment plot in Huang2 disclose only one major peak in a 180° field. The two FFT plots are perfectly consistent.

41. Dr. Mikos also points to the difference in shape and absolute height between the FFT alignment plot in my original declaration (*Id.*) and the FFT alignment plot in Huang2. (EX2015, ¶¶88-89.) Those differences exist because of the exact image tested. Indeed, Dr. Mikos acknowledges that the FFT plot in Huang2 may represent the average plot of separate FFT analysis run on five different images taken of different parts of the scaffold. (*See id.*, ¶¶80-81; EX1220, 100:7-101:7.) Huang2 did this because its authors had more data. In contrast, I ran an FFT on the only image that was provided in Huang2 because that was all that was available. Contrary to Dr. Mikos's assertions that this renders my testing deficient, this difference explains why Huang2's FFT alignment plot is not identical to the FFT alignment plot in my original declaration (EX1003, ¶110). And Dr. Mikos's discussion of the strength at failure increasing above a threshold peak height misquotes Ayres 2008, which was discussing a gelatin scaffold. (EX2015, ¶89 (citing EX1010, 610).) Ayres 2008 actually discloses that experiments have to be conducted to determine how differing peak heights affect each polymer. (*See* EX1010, 619-20.)

42. Dr. Mikos identified four peaks in my FFT testing of Huang2. (EX1220, 107:9-12, 110:9-11.) I disagree with Dr. Mikos because, in my opinion, the “peaks” at 0 and 180 correspond to background noise. And, in fact, my analysis of Huang2 is completely consistent with what is depicted in the Huang2 paper and detected the same fiber orientation as reported by Huang2. However, if you apply Dr. Mikos’s arithmetic mean test to the four peaks he identified at his deposition (*id.*) it would satisfy even his arithmetic mean test. If you consider the noise as peaks, the peak heights are 0.51, 0.27, 0.53, and 0.25, according to the data I obtained from running the FFT according to Ayres 2008. The arithmetic mean is 0.39. Thus, even under Dr. Mikos’s arithmetic mean test, there are two major peaks in Huang2, the peak at 90 and 270. These peaks are separated by 180 degrees, and thus have the claimed peaks.

B. Huang2 Anticipates Dependent Claims 2-3 and 5-12

43. Dr. Mikos only specifically addresses claims 2 and 3. Since I am only addressing his comments in this declaration, I am also only specifically addressing claims 2-3. It remains my opinion that claims 2-3 and 5-12 are anticipated by Huang2 for the reasons set forth in my prior declaration. (EX1003, §§VI.A.2-3, 5-12.)

44. Claim 2 requires that the fibers comprise type 1 collagen in its native triple helical structure. (EX1001, cl. 2.) My opening declaration explains that

Huang2's use of type 1 collagen as a *starting material* meets this claim element. (*Id.*, ¶117.) Dr. Mikos argues the collagen is not in triple helical form *after* being electrospun. (EX2015, ¶107.) In my opinion, the claim does not require that the collagen remains in its triple helical form after being electrospun. Consistent with that reading, the patent has no teaching related to maintaining the collagen in its native form and its only teaching related to collagen is including collagen as a possible starting material. (*E.g.*, EX1001, 14:27-34.) The patent doesn't report the structure of collagen after electrospinning.

45. In addition, I disagree with Dr. Mikos's other arguments. Dr. Mikos argues that the solvent used by Huang2, HFIP, breaks down the collagen. (EX2015, ¶¶112-13.) But the patent also uses HFIP (*E.g.*, EX1001, 19:40-55 (example 1)), and Dr. Mikos published in the prior art, citing one of my papers, that even after electrospinning using HFIP as a solvent, the electrospun collagen still "possessed the typical 67 nm banding pattern observed in *native collagen*." (EX1209, 1205 (emphasis added); EX1220, 135:3-14, 141:4-142:2.) This means that the collagen was not denatured and remains in its triple helical form. (EX1015, 3782.) As I published, and as Dr. Mikos published, I continue to believe that even after electrospun, type I collagen will maintain its native structure.

46. In addition, I note that Dr. Mikos testified that the heart basement membrane used for electrospinning in the '223 patent is comprised of Type 1

collagen. (EX1220, 124:1-4.) I disagree. Heart basement membrane does not contain Type 1 collagen, which instead is part of the extracellular matrix that surrounds the heart basement membrane. In fact, the heart basement contains type IV collagen, which does not form fibers in the body, and instead forms sheets.

47. Dr. Mikos also argues that the acid by-products of PCL will break down the collagen (EX2015, ¶110), but again, the '223 patent suggests using blends of collagen and PCL without any explanation how to maintain the structure of the collagen after electrospinning. (EX1001, 9:60-65, 19:40-23:4 (Examples 1-4).) And Dr. Mikos cited prior art demonstrating that PCL was stable for 3-4 years, so it will not interfere with collagen in a meaningful way for years, if at all. (EX2018, Abstract.) And Dr. Mikos criticism was that the PCL will only interfere with the triple helix during storage. (EX2015, ¶110.) Under my reading of the claims, the claims do not require a triple helical structure after years of storage, and there is nothing in the patent that states this either

48. Dr. Mikos also argues that the fetal bovine serum ("FBS") in Huang2 eliminates the triple helical collagen. (EX2015, ¶111.) But FBS is used for cell culture in Huang2 (EX1005, 1792 (§2.3, Cell seeding and culture onto nanofibrous matrix)), claim 2 does *not* require cell culture (EX1001, cl. 2), and Huang2's scaffold is made without cells and without the use of FBS (EX1005, 1792 (§2.2, Nanofibrous matrix preparation). The fact that Huang2 subsequently cultures cells

on it is irrelevant. (EX1005, 1792 (§2.3, Cell seeding and culture onto nanofibrous matrix.) The '223 patent also does not require cells to be cultured on it. (EX1001, 1:10-18.) As I read the patent, culturing cells is a separate and different aspect of the invention the patent is describing. The patent states: “The invention *further relates* to methods culturing cells on the scaffold or aligned fiber described herein. *In some embodiments*, the cells are selected from the group consisting of stem cells, adipose derived stem cells, dental pulp stem cells, fibroblasts, and dorsal root ganglia.” (*Id.*, 16:3-7 (emphasis added).) Based on my understanding of the claims, this aspect of the invention is claimed in independent claim 11. (EX1001, cl. 11.)

49. I note that the applicants for the patent, made this point during prosecution of the related '227 patent. The applicants argued that “[r]egarding growing or culturing cells, Applicant submits that the invention disclosure provides that including cultured cells is an *alternative feature*.” (IPR2025-00249, EX1002, 652 (emphasis added).) The applicant further argued the “invention *optionally* offers cell culturing.” (*Id.* (emphasis in original).) In support of this argument, applicants quote the following text that is also in the '223 patent at column 18, lines 32-40:

Applicant’s invention also relates to methods of treating a tissue or organ defect or injury, for example, a musculoskeletal, dental or soft-tissue defect or injury, in an animal comprising administering (1) cells cultured on the scaffold produced by the methods described herein and/or (2) the aligned fiber, electrospun fiber, scaffold and/or implant

described herein to the tissue or organ defect (e.g. osseous defects, defects in cartilage, ligament, tendon, spinal disk, and tendon insertion site to bone) (*id.*, [0101]).

(*Id.*, 653.)

50. Claim 3 requires the scaffold to have less than 8% residual calcium by weight. (EX1001, cl. 3.) Dr. Mikos argues that the calcium content in Huang2's scaffold could be greater than 8% by weight because the collagen *could* have been isolated using reagents comprising calcium. (EX2015, ¶¶118-19.) Dr. Mikos does not and cannot argue that the standard way for obtaining collagen uses calcium, let alone yields a product that is sold as collagen, but contains 8% by weight of calcium. Further, my understanding of claim 3 is that it does not require the culturing of cells on the scaffold. Huang2 makes a scaffold without cells on it. (EX1005, 1792 (§2.2, Nanofibrous matrix preparation). Thus, the fact that Huang2 subsequently cultures cells on it with FBS is irrelevant. (*Id.* (§2.3, Cell seeding and culture onto nanofibrous matrix.) Additionally, Dr. Mikos's arguments concerning the presence of calcium in FBS as a source of the collagen are incorrect for the same reasons set forth in ¶¶48-49, above.

III. HUANG2 AND KUMBAR RENDER CLAIM 4 OBVIOUS

51. Claim 4 requires an "average porosity from about 60% to about 90%." (EX1001, cl. 4.) Dr. Mikos argues that Kumbar's porosities do not apply to Huang2. (EX2015, ¶131.) I disagree.

52. A POSA would have known that Mikos's teaching of what "high" porosity is applies to Huang2's electrospun scaffold. As I discussed in my original declaration, Huang2 states that high porosity is a desirable quality in an electrospun scaffold and cited to Kumbar for this proposition, which provided examples of electrospun scaffolds that have porosity within the claimed range. (EX1003, §VI.B.)

53. Dr. Mikos also argues that a POSA would not have had a reasonable expectation of success in modifying Huang2 to achieve the claimed porosities. (EX2015, ¶140.) I disagree.

54. A POSA would have known that routine electrospinning parameters could be changed to alter porosity. The prior art established that fiber size is the most important factor in obtaining a high porosity. (EX1214, 7; EX2015, ¶131; EX2017, 44:16-18.) And there are many publications, including by Dr. Mikos, where the authors adjusted fiber size by adjusting the parameters used for electrospinning. (*E.g.*, EX1006, 2; EX1215, 2800, 2804; EX1010, 618 ("fiber diameter and pore dimension of a given polymer scaffold can be largely controlled" by altering routine parameters).) In fact, Dr. Mikos, in scaffolds made of PCL, was able to predict and obtain the desired fiber size just by routinely alternating the parameters for electrospinning. (EX1215, 2800, Tables 1-2, 2804

(“We demonstrated the ability to fabricate 3D microfiber scaffolds with controlled fiber diameters up to 10 um.”); EX1220, 157:2-15, 158:25-159:13.)

55. Consistent with these publications, the prior art plainly taught aligned scaffolds that have the claimed porosity. (EX1211, 7, Table 2 (aligned electrospun scaffold with 75.7% porosity); EX1212, 120-22, Figure 6 (showing aligned scaffolds with porosities ranging from 81-88%); EX1213, 1207, Table 1 (aligned scaffolds with porosities ranging from 74.85-78.57%.))

56. The '223 patent itself demonstrates that controlling the porosity was within the skill of a POSA. The only teaching of porosity in the patent appears at column 14, lines 21-26, where it states ranges of potential porosity values that range from a low of 60% to a high of 95%. (EX1001, 14:21-26.) There is no teaching how to obtain such porosity in aligned fibers. Given that there is no teaching, this suggests that a POSA would know how to obtain such ranges based on the prior art.

57. Further, and contrary to Dr. Mikos's implications (EX2015, ¶124 (“the porosity of a scaffold cannot be known without being specifically measured”)), measuring porosity is a conventional routine process in the prior art. In a published paper, Dr. Mikos measured the porosity of scaffolds by three different methods and concluded that all “measured porosities were between 84% and 89%, regardless of the measurement technique selected.” (EX1215, 2800.)

58. Thus, it is my opinion that a POSA would have been motivated to obtain an aligned scaffold with the claimed porosity and have expected success in being able to do so.

IV. LEE ANTICIPATES CLAIMS 1-12

A. Claim 1 is Anticipated

1. Lee's Highly Aligned Fibers Have the Peaks Recited in Claim 1

59. My opening declaration explained that Lee discloses fibers with the claimed FFT to a POSA by disclosing aligned fibers, which by definition, must have two major peaks in the FFT 180° from each other. I explained that “[a]s I discussed above, an FFT analysis measures the degree of fiber alignment, and an FFT result showing fibers having adjacent major peaks with about 180° apart from each other *only occurs when the fibers are aligned.*” (See EX1003, §VI.C.1.c., ¶181 (emphasis added).) Ayres 2008, incorporated into the ’223 patent, also explains that “FFT alignment plots generated from sample scaffolds containing aligned elements *exhibit . . . two larger peaks at 90 and 270° . . .*” (EX1010, 610 (emphasis added).)

60. Thus, a POSA would have known and understood that highly aligned fibers, such as those prepared by Lee, will have the peaks recited in the claim. (*Id.* (“The 2D FFT alignment 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).”).)

61. Lee obtained highly aligned collagen blended fibers, and demonstrated it by multiple methods, including fiber orientation testing using computer analysis, mechanical testing, and visual inspection. (EX1003, ¶¶181-85, 191.) I also provided FFT testing that further confirmed that the fibers are aligned that are consistent with Lee’s results. (*Id.*, ¶¶186-90.) And Dr. Mikos does not challenge that Lee obtained highly aligned collagen blended fibers. (EX2015, ¶190 (“Lee does not express any doubt regarding the alignment of its fibers.”); EX1220 at 192:6-15.)

62. I also explained that my FFT testing, which showed two major peaks 180° apart, was “a natural and necessarily present property of the fibers Lee discloses.” (EX1002, ¶190.) Thus, Lee discloses the FFT element of the claims.

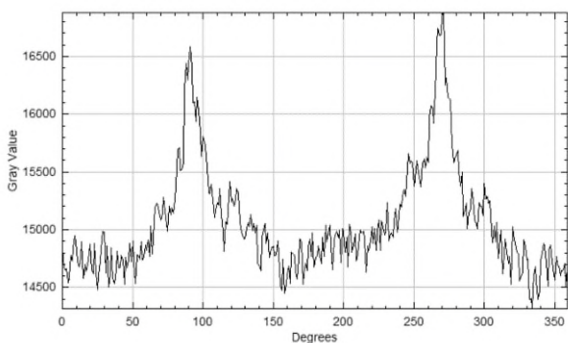
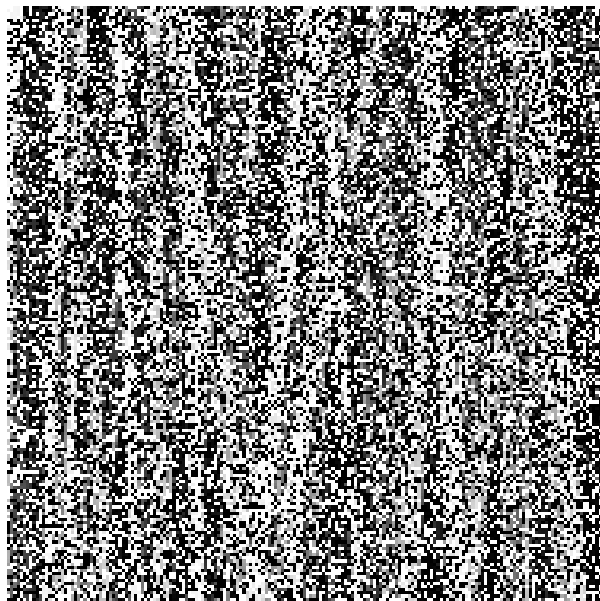
2. Dr. Mikos’s Criticisms of the FFT Testing of Lee in My Original Declaration Lack Merit

63. Dr. Mikos also does not dispute that the testing of Lee in my original declaration discloses the claimed FFT peaks. Instead, Dr. Mikos criticizes how the FFT testing was conducted. These criticisms are mostly the same as those concerning the Huang² testing, and my responses above apply equally here. (EX2015, ¶¶146-61; *supra* §II.A.) Dr. Mikos’s main challenge seems to be that the

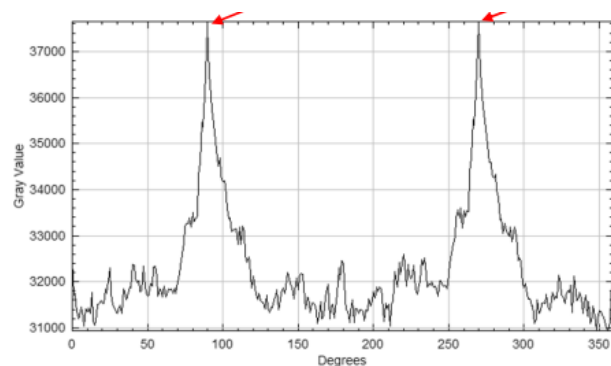
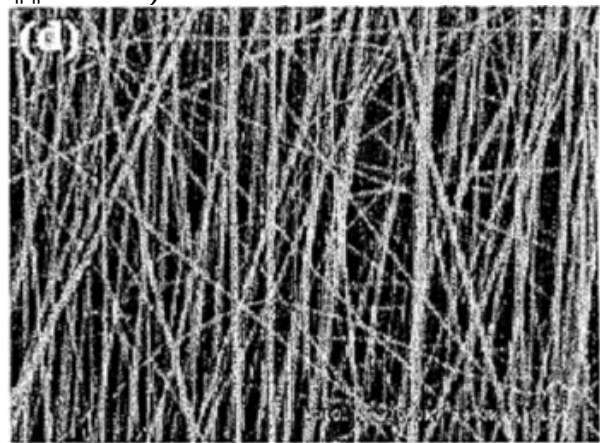
image that was analyzed is too low quality (EX2015, ¶152) so it is “unsuitable for analysis,” but as mentioned above, I conducted additional experiments showing that large amounts of noise do not stop an FFT from demonstrating the claimed FFT peaks if the fibers are in fact aligned. (*Supra* §II.A.) The results demonstrate that a considerable amount of noise does not alter the presence of two alignment peaks.

64. I note that the last image from my noise test, which has the most noise, still demonstrates two major peaks in its FFT alignment plot. That image is much noisier than the image that I used for the Lee analysis. The last image from the noise test and its FFT alignment are below, as well as the image from Lee. (EX2015, ¶164.)

Data generated by adding noise to Huang2's image and creating an FFT alignment plot according to Ayres 2008 (*supra* ¶35)



Data generated from the image in Lee and creating an FFT alignment plot according to Ayres 2008 (EX1003, ¶¶184-90)



(EX1003, ¶184)

(EX1003, ¶188)

B. Lee Anticipates Dependent Claims 2-12

65. Dr. Mikos only offers additional arguments concerning dependent claims 2, 3, 4, and 12. Dr. Mikos's arguments concerning claims 2 and 3 are the same as with regard to Huang² and fail for the same reasons discussed above. (*Supra* §II.B.)

66. Regarding claim 4, my opening declaration explains that Lee discloses that, in some embodiments, its electrospun nanofiber scaffolds have high porosity, and incorporates Mikos in its entirety, which discloses that high porosity is greater than 80% by volume. (EX1003, ¶90.) This plainly falls within the claimed range of 60% to 90%, which I understand means that it anticipates the claims.

67. Additionally, as discussed above, the '223 patent is silent about how to achieve the claimed porosity, relying on the skill of a POSA to achieve the claimed range. This demonstrates that a POSA would have been able to achieve the claimed range.

68. Claim 12 requires a method of culturing cells on the scaffold, where the cells may be "stem cells." (EX1001, cl. 12.) Lee discloses culturing "skeletal muscle cells" on its scaffold. (EX1011, [0007]), and teaches that "[s]keletal muscle cells include . . . myoblasts . . ." (*id.*, [0040].) Contrary to Dr. Mikos's assertions that myoblasts are not stem cells (EX2015, ¶¶186-88), Lee itself discloses that "'myoblasts' are a type of muscle stem cell." (EX1011, [0030]; EX1003, ¶239.) I

agree. In fact, prior art publications stated that “[m]yoblasts are defined as stem cells containing skeletal muscle precursors.” (EX1217, 455.)

V. LEE RENDERS CLAIMS 1-12 OBVIOUS

69. A POSA would have been motivated to use FFT to confirm the alignment of Lee’s fibers using FFT with a reasonable expectation of success.

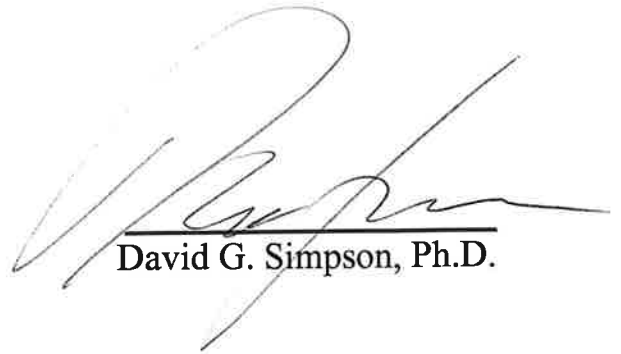
70. Dr. Mikos admits that FFT was a well-known conventional technique (EX1220, 31:10-32:7), but still argues that there would have been no motivation to run a FFT on Lee’s fibers because already Lee confirmed that the fibers are highly aligned. (EX2015, ¶190.) But Dr. Mikos ignores that the techniques used in Lee to analyze the alignment fibers (analysis of an SEM image and mechanical testing) are both *destructive* of the scaffold just created. (EX1011, [0065]-[0067]; EX1220, 54:5-8, 56:13-57:9.)

71. One of the advantages of using FFT to measure alignment, and contrary to Patent-Owner’s assertions (POR, 47), it is *non-destructive*. (EX1003, ¶11; EX1220, 55:5-17.) And it can be used on a brightfield image, which is a non-destructive method to obtain an image of the fibers. (See EX1010, 608, 620.) Thus, if a POSA followed the techniques of Lee to engineer a scaffold that could be used to treat a tendon injury, for example, and wanted to confirm the fibers prepared are in fact aligned, then FFT would have been used by a POSA to do so. As I discussed in Ayres 2008, FFT is a simple, non-destructive technique, allowing the POSA to

then use the scaffold to subsequently treat the injury. (EX1010, 620.) Indeed, the method in Ayres 2008 is well-known and common in the field. Ayres 2008 was cited 360 times. (EX1222.) Likewise, Ayres 2006, which discloses the same method, was cited 395 times. (EX1223.)

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

Date: February 3, 2026



David G. Simpson, Ph.D.

Appendix A

Exhibit No.	Description
1001	U.S. Patent No. 10,137,223 to Francis et al. (“the ’223 patent”)
1003	Declaration of David G. Simpson, Ph.D.
1004	CV of David G. Simpson, Ph.D.
1005	Huang et al., <i>The involvement of integrin $\beta 1$ signaling in the migration and myofibroblastic differentiation of skin fibroblasts on anisotropic collagen-containing nanofibers</i> , 33 Biomaterials 1791-1800 (Feb. 2012) (“Huang2”) (available online Dec. 2, 2011)
1006	Kumbar et al., <i>Electrospun nanofiber scaffolds: engineering soft tissues</i> , Biomed. Mater. 3 (2008) (“Kumbar”)
1008	Huang et al., <i>Electrospun collagen-chitosan-TPU nanofibrous scaffolds for tissue engineered tubular grafts</i> , 82 Colloids and Surfaces B: Biointerfaces 307-315 (2011) (“Huang1”)
1009	U.S. Patent App. Pub. No. 2004/0037813 to Simpson et al. (“Simpson”)
1010	Ayres et al., <i>Measuring fiber alignment in electrospun scaffolds: a user’s guide to the 2D fast Fourier transform approach</i> , 19 J. Biomater. Sci. Polymer. 603-621 (2008) (“Ayres 2008”)
1011	Lee et al., U.S. Patent Application No. US 2010/0331980 A1, Pub. Date December 1, 2011 (“Lee”)
1013	Ayres et al., <i>Modulation of Anisotropy in Electrospun Tissue-Engineering Scaffolds: Analysis of Fiber Alignment by the Fast Fourier Transform</i> , 27(32) Biomaterials 5524-5534 (2006) (“Ayres 2006”)
1014	U.S. Pat. No. 5,514,378 to Mikos (“Mikos”)
1015	Jose et al, <i>Fabrication and Characterization of Aligned Nanofibrous PLGA/Collagen Blends as Bone Tissue Scaffolds</i> , 50 Polymer 3778-85 (2009) (“Jose”)
1016	Fu et al, <i>Spatial Arrangement of Polycaprolactone/Collagen Nanofiber Scaffolds Regulates the Wound Healing Related</i>

	<i>Behaviors of Human Adipose Stromal Cells</i> , 18(5) Tissue Engineering, 631-42 (2012) (“Fu”)
1017	Shoulders & Raines, <i>Collagen Structure and Stability</i> , 78 Annu. Rev. Biochem. 929 (2009)
1018	Kuo et al., U.S. Patent Application No. US 2011/0293685 A1, Pub. Date Dec. 1, 2011 (“Kuo”)
1019	Beachley et al, <i>Highly Aligned Polymer Nanofiber Structures: Fabrication and Applications in Tissue Engineering</i> (2011) in Vol. 246 Biomedical Applications of Polymeric Nanofibers (Jayakumar & Nair eds. 2011)
1020	Declaration of Emma Xu
1021	U.S. Provisional Patent App. No. 61/0255,35 (“Lee Provisional”)
1203	Smoak et al, <i>Bioinspired Electrospun dECM Scaffolds Guide Cell Growth and Control the Formation of Myotubes</i> , 7(20) Sci Adv at 1 (May 2021)
1209	Pham et al, <i>Electrospinning of Polymeric Nanofibers for Tissue Engineering Applications: A Review</i> , 12(5) Tissue Engineering 1197 (2006)
1211	Subramanian et al, <i>Fabrication of Uniaxially Aligned 3D Electrospun Scaffolds for Neural Regeneration</i> , 6(2) Biomed. Mater. 1 (2011)
1212	Sell et al, Scaffold Permeability as Means to Determine Fiber Diameter and Pore Size of Electrospun Fibrinogen, 85(1) J. Biomed Mater Res A 115 (2008)
1213	Meng et al, <i>Electrospinning of PLGA/Gelatin Randomly-Oriented and Aligned Nanofibers as Potential Scaffold in Tissue Engineering</i> , 30(8) Materials Science and Engineering C 1204 (2010)
1214	Srinivasan et al, <i>Multiscale Fibrous Scaffolds in Regenerative Medicine</i> , 246 Adv Polym Sci 1 (2012)
1215	Pham et al, <i>Electrospun Poly(ϵ-caprolactone) Microfiber and Multilayer Nanofiber/Microfiber Scaffolds: Characterization of</i>

	<i>Scaffolds and Measurement of Cellular Infiltration</i> , 7(10) Biomacromolecules 2796 (2006)
1217	Liu et al, <i>Myoblast Therapy: From Bench to Bedside</i> , 15 <i>Cell Transplantation</i> 455 (2006)
1220	Transcript of January 21, 2026 Deposition of Dr. Antonios G. Mikos
1222	Excerpt from Google Scholar, https://scholar.google.com/scholar?hl=en&as_sdt=0%2C47&q=ayres+2008+fft&btnG= (last visited, 2/2/2026)
1223	Excerpt from Google Scholar, https://scholar.google.com/scholar?hl=en&as_sdt=0%2C47&q=ayres+2006+fft&btnG= (last visited, 2/2/2026)