

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

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

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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 ’227 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 ’227 patent, Kuo, 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, ¶¶57-58.) 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." (*Id.*, ¶ 55 (citing EX1001, 13:28-29).)

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 '227 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.

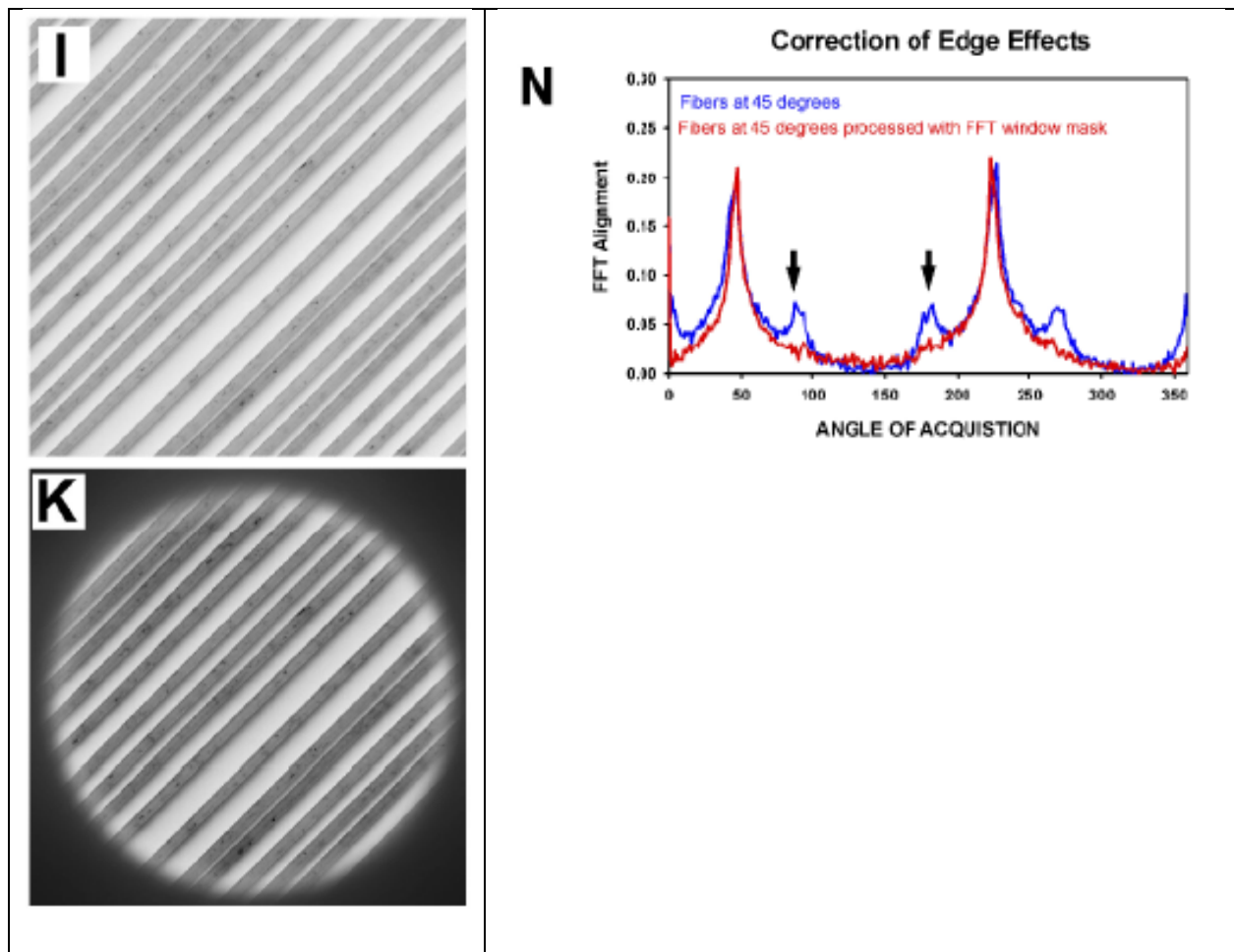
9. In fact, in my review of the prior art in this case, I have not seen any publications (including Huang1 and Huang2) that carry out Dr. Mikos's test to identify major peaks and fiber alignment. And Dr. Mikos testified that he has also not seen any prior art that uses his arithmetic mean test. (EX1220,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

10. There is also no evidence in the '227 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 '227 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 '227 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.) 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 '227 patent only has two alignment plots, Figures 8A and 8B. Dr. Mikos states that, as indicated by the '227 patent, Figure 8A in the '227 patent shows aligned fibers but Figure 8B shows "random fibers." (EX2015, ¶51 (citing EX1001, 13:46-49).) 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 (see EX2015, ¶50) 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 '227 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. KUO AND HUANG2 RENDER THE CLAIMS 1-6 OF THE '227 PATENT OBVIOUS.

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 '227 patent. (EX1003, ¶¶125-26.)

22. The plot from my earlier declaration is below. (*Id.*, ¶125.)

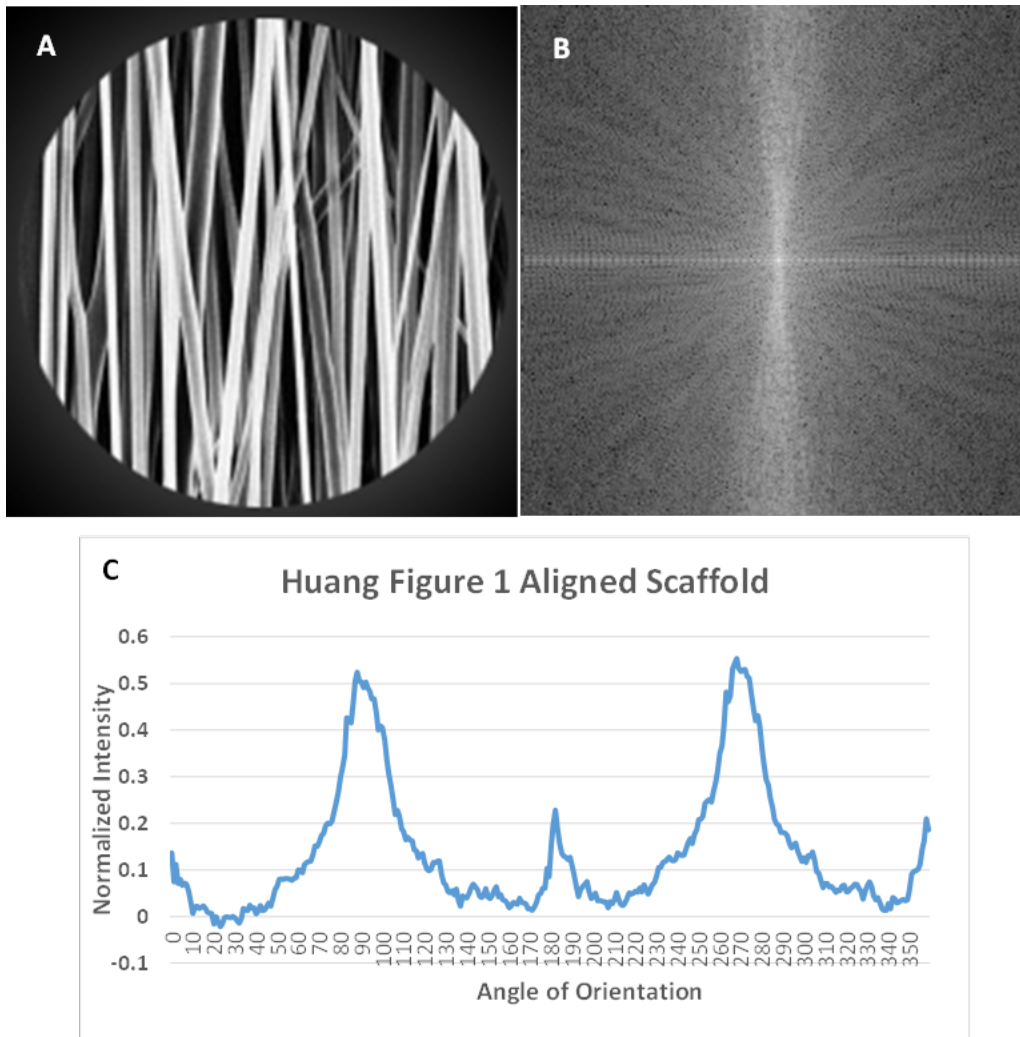


Figure 2. (A) Figure 1 from Huang aligned scaffold cropped and masked for 2DFFT. (B) 2DFFT spectrum of aligned scaffold, the image has been rotated to correct for the rotation intrinsic to the FFT analysis. (c) Normalized intensity values for aligned scaffold 0-360 degrees.

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, ¶¶84-114.) 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 '227 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, ¶104), the image type used in my analysis (*id.*, ¶105), illumination (*id.*, ¶106), noise (*id.*, ¶107), software version (*id.*, ¶173), normalization (*id.*, ¶111), and masking (*id.*, ¶112).

28. I performed my analysis according to Ayres 2008, which is the level of detail provided in the '227 patent. (EX1001, 13:38-49.) Dr. Mikos acknowledges that none of the details he pointed to are spelled out in the '227 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, ¶104), 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 (Fig. 1B)).

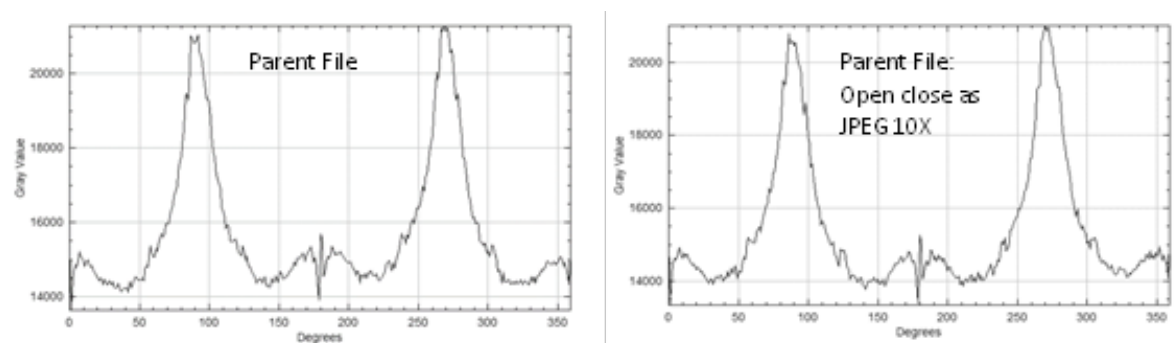
30. Regarding the image type (EX2015, ¶105), the only reason to use a specific image is to preserve image quality (EX1010, 607). I testified that the

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 did 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 show 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

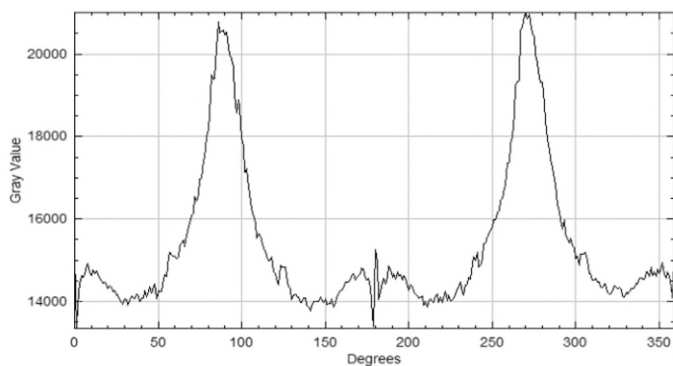
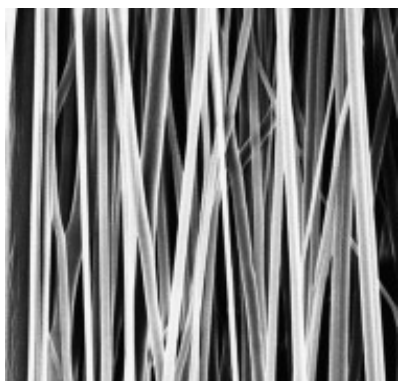
compress images, leading to a loss in quality that you can't regain. Visuals saved as PDF are of very high quality and even customizable, making them the file format of choice for printers.”)

34. Regarding illumination (EX2015, ¶106), 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.

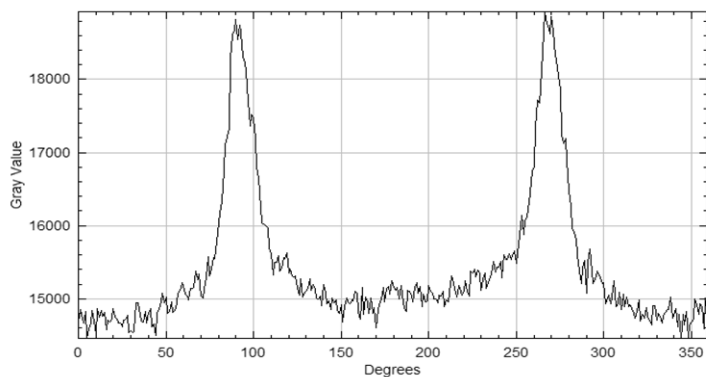
35. Regarding noise (EX2015, ¶107), it is my opinion that the image I downloaded for Hunag2 is very clear and does not possess “noise” that would preclude me from running a scientifically valid FFT. In addition, I have now run additional tests to show the effects of noise. To do this, I sequentially 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.

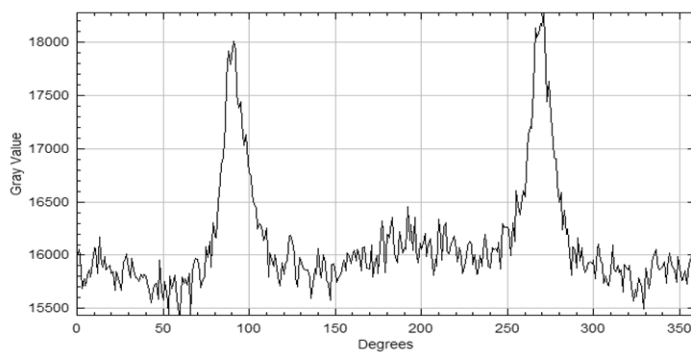
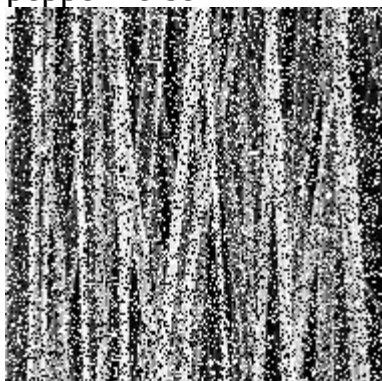
No noise



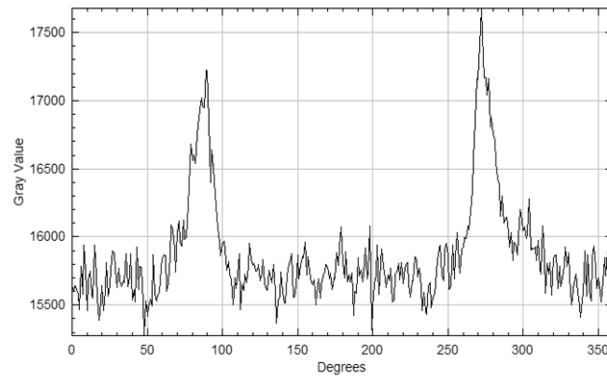
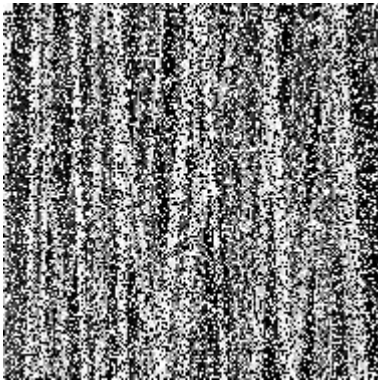
2 cycles of salt and
pepper noise



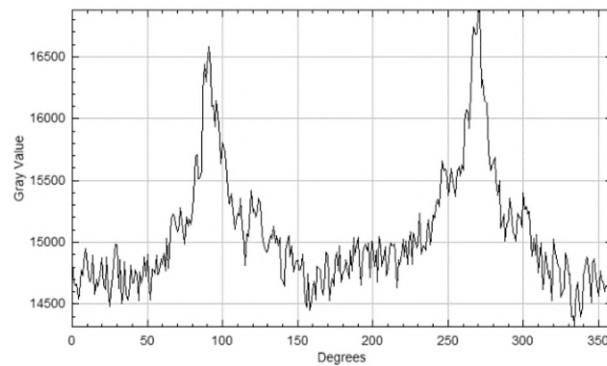
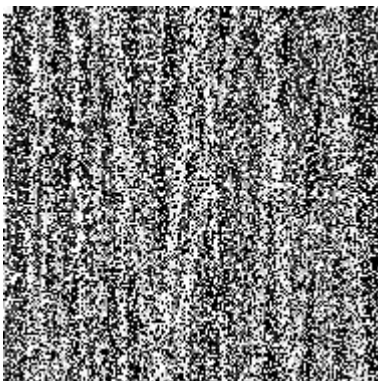
10 cycles of salt and
pepper noise



15 cycles of salt and
pepper noise



20 cycles of salt and
pepper noise

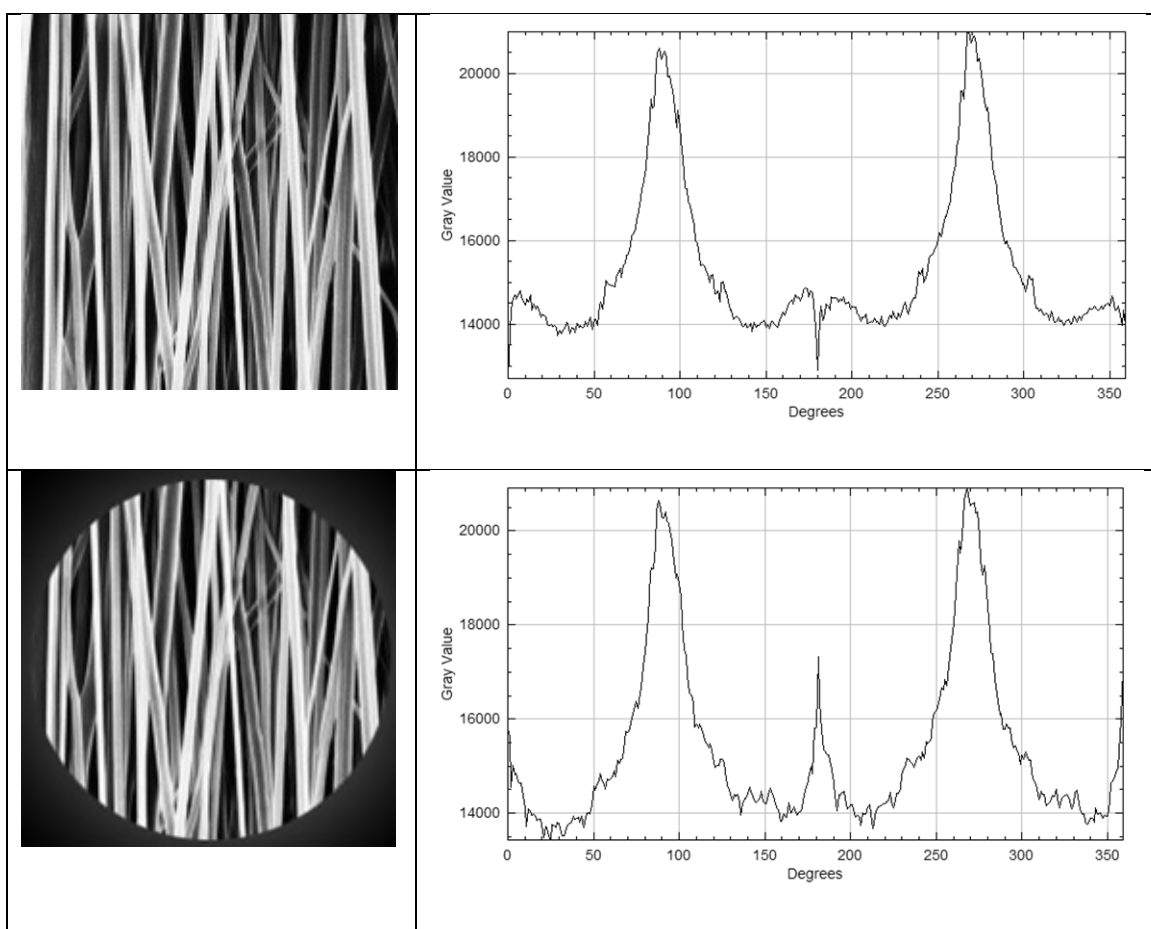


36. Regarding software version (EX2015, ¶173), it not important to know the version (EX2017, 161:16-21), I used the most recent version, and that all that matters is that the version had been corrected in line with Ayres 2008 (*id.*, 141:10-19). Some early versions of the program used unit circle with 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 '227 patent. (See EX1010, 607; EX1001.)

37. Regarding normalization (EX2015, ¶111), 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.*, ¶112), 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 '227 patent, whose only discussion of FFT analysis is incorporating Ayres 2008 by reference. (EX1001, 13:38-49.) 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, ¶¶96-

101.) 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, ¶¶125-26.) Dr. Mikos points to the lack of minor “peaks” in Huang2. (EX2015, ¶100.) But, as set forth in Ayres 2008, smaller peaks, like the ones in the FFT alignment plot in my original declaration (EX1003, ¶125), 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, ¶125) 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, ¶¶98-99.) 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.*, ¶¶90-91; 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, ¶125). 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, ¶99 (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. A Skilled Artisan Would Have Been Motivated to Use the Aligned Fibers of Huang2 to Treat a Tendon, Ligament, or Nerve as Taught by Kuo

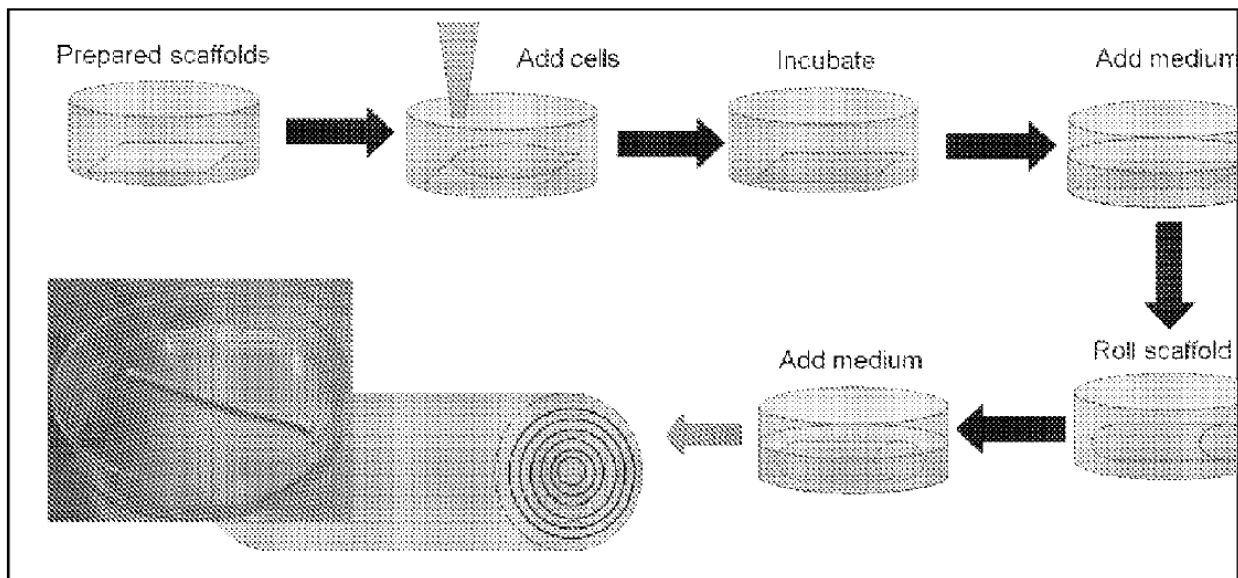
43. As an initial matter, the '227 patent does *not* contain any actual examples of treating a tendon, a ligament, or a nerve with aligned collagen fibers. (EX1220, 192:20-194:17; EX1001, 19:64-23:27 (Examples 1-4).) Thus, the '227 patent relies on the state of the art in treating such injuries. As I read the '227 patent, it does not teach any contributions to treating a tissue injury beyond what was known in the art. As discussed in my original declaration, and below, the prior art teaches far more than the '227 patent and renders obvious the treatment of a tendon, ligament, or nerve injury with the aligned fibers of Huang2.

1. Dr. Mikos is Wrong That a POSA Would Not Be Motivated to Combine Huang2 and Kuo

44. Dr. Mikos argues that a POSA combining Huang2 and Kuo would use a scaffold comprising of dermal fibroblasts, according to Huang2, and then use such a scaffold to treat a tendon, ligament, or nerve injury. (EX2015, ¶116 (bullet three).) Dr. Mikos provides a series of arguments for why this would not work and that there would thus be no motivation to combine Huang2 and Kuo. (*Id.*, ¶¶117-42.)

45. I do not agree with Dr. Mikos. As my original declaration explained that “a POSA would have been motivated and expected success in creating a

scaffold comprising Huang2's *aligned fibers*—as shown by FFT analysis—containing collagen, which may be crosslinked, such that they can be used to treat a tendon, ligament, or nerve defect *as taught by Kuo*" (EX1003, ¶97 (emphasis added).) Kuo discloses a "schematic showing fabrication of a tissue construct," containing several steps, that can be used to repair a tissue injury. (EX1018, Fig. 1, [0022], [0028].)



46. As I explained in my original declaration, the very first step of the Kuo schematic, as shown in Fig. 1, is to start with a flat "scaffold sheet" of electrospun fibers, also referred to as a "mats" (EX1003, ¶130 (citing EX1018, [0022])); *see also* EX1018 at Fig. 1, [0005], [0007], [0020], Abstract; EX1220, 161:12-162:13.) Likewise, Kuo's own examples started with a flat sheet of

electrospun fibers to make constructs to treat a tendon or ligament injury. (EX1018, [0112]-[0113]).)

47. In making the flat sheet of electrospun fibers, Kuo teaches that “[e]lectrospinning can be performed by any means known in the art” (*id.*, [0044]), and discloses that “[e]lectrospinning for the formation of fine fibers has been actively explored recently for applications such as high performance filters and biomaterial scaffolds for cell growth, vascular grafts, *wound dressings* or *tissue engineering*” (*id.*, [0046] (emphasis added)). Huang² is in the field of tissue engineering, and Dr. Mikos even characterizes Huang² as addressing “skin wo[und] repair.” (EX2015, ¶115; EX1220, 164:8-165:15.) Additionally, Kuo expresses a preference for highly aligned fibers. (EX1018, [0112]-[0113].) Thus, Kuo provides the motivation for a POSA to look at the electrospinning art in the wound dressing space to find the best techniques to make highly aligned fibers.¹

48. The search that a POSA would have undertaken would have yielded Huang², which teaches an aligned electrospun scaffold for cell growth, wound

¹ While Kuo claims it prepared aligned collagen fibers, Kuo provides no testing evidence that it obtained an aligned scaffold.

healing, and tissue engineering. (See EX1005, Abstract.) Huang2's electrospinning techniques yield highly aligned electrospun collagen blended fibers, which Kuo teaches is preferred (EX1018, [0112]-[0114]). Beyond that, Huang2 proved the alignment of its fibers scientifically, using both FFT analysis and mechanical testing, the gold standard test for determining anisotropic materials. (EX1005, 1794; EX1003, ¶¶117-27.) Further, there would have been a reasonable expectation of creating the flat scaffold sheet as both Huang2 and Kuo were able to make such sheets. Thus, there was plainly motivation to use the flat sheet aligned scaffold of Huang2 as the first step of the Kuo process discussed in Fig. 1 and paragraphs 20, 22. (See EX1018, Fig. 1, [0020], [0022].)

49. The next step of the Kuo process is seeding the “[p]repared scaffolds” with cells. (*Id.*, Fig. 1 (“add cells”); *see also id.*, [0022] (“contacting a scaffold sheet of fibrous material with a cell”).) Dr. Mikos asserts that one would **only** seed the scaffold made by the techniques of Huang2 with dermal fibroblasts to treat, for example, a tendon injury (*see* EX2015, ¶116 (bullet three), ¶135). I disagree. A POSA combining Huang2 and Kuo would take the flat sheet made by the techniques of Huang2 and, according to Kuo, seed it with the appropriate cells that *correspond* to the tissue injury one would like to treat. Kuo unambiguously teaches that “any cells may be employed that are found in the natural tissue to which the *construct is intended to correspond.*” (EX1018, [0058] (emphasis added).) Dr.

Mikos even admits that one step of the process is to seed “appropriate cells onto a scaffold.” (EX2015, ¶118.) Kuo lists different types of cells that correspond to different tissues that can be repaired, such as a tendon or ligament. (*Id.*) As I discussed in my opening declaration, “a POSA would have been able to make and use a scaffold comprising Huang2’s aligned fibers and *seeded with various cell types* using well-known established methods described in both Huang2 and Kuo to achieve predictable results with a reasonable expectation of success.” (EX1003, ¶102 (emphasis added).)

50. The third step of Kuo’s process is to take the electrospun collagen blended scaffold sheet, now seeded with the desired cells, and roll the sheets to approximate the structure of a tendon or ligament. (EX1018, Fig. 1 (“roll scaffold”); EX1220, 160:5-15.) Kuo followed this process in the examples—it rolled the flat sheets after seeding it with cells. (EX1018, Fig. 1; *see also id.* at [0022] (“rolling the scaffold sheet in a jelly-roll like manner to form a spirally wound tissue construct”).) Thus, contrary to Dr. Mikos’s assertions (EX2015, ¶¶117-24), based on the straightforward teaching of Kuo, a POSA would have motivated to take the seeded electrospun flat scaffold made by the techniques of Huang2 and roll it to treat a tendon and ligament.

2. Dr. Mikos Is Wrong that Huang2's Teachings Are Limited to Skin Repair

51. Dr. Mikos also argues that Huang2 is a reference discussing the treating the healing of wounds to the skin using a scaffold containing dermal fibroblasts and thus has no relevance to tendon or ligament repair. (EX2015, ¶¶134-42.) One of the main purposes of Huang2, however, is to explore how the alignment of collagen fibers affects the differentiation of fibroblasts to myofibroblasts. (EX1005, Abstract (“Moreover, the fibroblast-to-myofibroblast differentiation was greatly enhanced for the [normal human dermal fibroblasts] NHDFs cultured on anisotropic nanofibrous matrices over a period of 48 h.”); EX1220, 104:6-105:10.) The differentiation of fibroblasts to myofibroblasts is one of the essential healing pathways in treating many tissue injuries in the body, including the connective tissues of the dermis of skin, tendon, and ligament. (EX1005, 1792; EX1220, 105:12-106:7; EX1204.) Huang2 electrospun both highly aligned fibers and random fibers and reported that the aligned fibers “significantly promote the fibroblast-to-myofibroblast differentiation” (EX1005, 1797.)

52. Accordingly, a POSA would have understood that the teachings of Huang2 were relevant to treating all connective tissue, including tendon and ligament, not just wounds in the connective tissue layer of the skin.

53. Beyond that, Dr. Mikos is incorrect when he argues that fibroblasts are “incapable of repairing tendon, ligament, or nerve defects.” (EX2015, ¶116 (bullet three); *see also id.*, ¶135.) Indeed, multiple research groups have used “skin-derived fibroblasts” to treat tendon and ligament injuries. (See EX1206, 1-2, 8-10; EX1207, 901.)

54. Liu is titled “Repair of Tendon Defect with Dermal Fibroblast Engineered Tendon in a Porcine Model.” (EX1205, 775.) There, the authors actually used dermal fibroblasts to treat a tendon injury in an animal model. Liu teaches that “[t]he result of this study demonstrated that tendons engineered by two different cell types exhibited similar features in their gross view, histology, and biomechanical property, indicating that *dermal fibroblasts may replace tenocytes for tendon engineering*. Importantly, *the dermal fibroblast engineered tendon* also resembled a natural tendon in its histological structure.” (*Id.*, 786 (emphasis added).) Dr. Mikos criticized the reference because it discloses treating an animal. (EX1220, 180:7-182:7). But I understand that applicant’s invention relates to “methods of treating . . . an animal.” (EX1001, 18:54-19:6; EX1002, 653.) Further, the authors and publishing journal accepted that the animal model used was an acceptable one.

55. Clarke studied the use of cells derived from dermal fibroblasts to treat tendons. (EX1206, 1.) The study suggests that the use of dermal fibroblasts is safe

and effective in treatment of tendon. (*Id.*, 10). The reason Clarke used dermal fibroblasts was that “[s]kin represents an abundant and accessible source of cells that can be used for cell therapy.” (*Id.*, 8.)

56. Eijk is titled “Tissue Engineering of Ligaments: A Comparison of Bone Marrow Stromal Cells, Anterior Cruciate Ligament, and Skin Fibroblasts as Cell Source.” (EX1207, 893.) Eijk studied the use of skin fibroblasts, among other cell types to treat ligament. Eijk concluded that skin fibroblasts possess the appropriate characteristics for application in ligament tissue engineering, whereas ACL fibroblasts did not. (*Id.*, 901.) This conclusion means that skin fibroblasts were more suitable for ligament repair than fibroblasts derived from ligament.

57. Accordingly, in responding to Dr. Mikos’ argument that a POSA would not have been motivated to combine Huang2 and Kuo to treat, tendon, ligament, and nerves (EX2015, ¶116), it is my opinion that a POSA would have been motivated to combine Huang2 and Kuo to do so for many reasons:

- Kuo begins with a flat, aligned electrospun scaffold comprised of blended PCL and collagen (EX1018, Fig. 1, [0113]–[0114]; EX1220, 161:11-162:14) and Huang2 teaches how to make such a sheet with verified aligned fibers (EX1005, 1792-93; EX1220, 96:13-15; EX1003, ¶102);

- Both Huang2 and Kuo discuss the importance of mimicking the extracellular matrix (“ECM”) of the native tissue being repaired (EX1003, ¶¶98; EX1005, 1791; EX1018, [0004]);
- Both Huang2 and Kuo specifically discuss the use of fibroblasts to repair tissue injuries (EX1003, ¶¶73, 86), a cell type that had actually been used to create scaffolds for tendon/ligament repair (*supra* ¶¶53-56);
- Huang2 studies the dermis, which is a connective tissue, (EX1220, 167:2-13), just like ligament and tendon (EX1003, ¶¶96);
- The dermis, tendon, and ligament are all populated by cells of the fibroblast lineage (*see* EX1207, 894);
- The dermis, tendon, and ligament are enriched in type 1 collagen (EX1003, ¶¶100; EX1018, [0003]; EX1205, Fig. 7, 785 (Fig. 7 caption));
- Huang2 demonstrated the ability to make aligned collagen fibers (EX1005, 1792-93; EX1220, 96:13-15; EX1003, ¶¶102), which characteristic of ligament and tendon (EX1003, ¶¶99);

- The dermis, tendon, and ligament heal through a process in which fibroblasts transform into myofibroblasts (EX1005, 1792; EX1220, 105:12-106:7; EX1204).

3. Dr. Mikos's Additional Challenges Are Without Merit

58. Dr. Mikos argues that a POSA would have been unable to use Huang2's scaffolds because its elastic modulus, stiffness, and degradation rate are insufficient. (EX2015, ¶¶125-33.) But the '227 patent itself presents no working examples of using a scaffold to treat tendon, ligament, or nerve and is *silent* about elastic modulus, stiffness, and degradation rate. Further, Dr. Mikos's modulus argument is based on the incorrect assumption that a POSA combining Huang2 and Kuo would use only dermal fibroblasts to treat a tendon injury. (*Id.*, ¶¶134-42.) As described above, that is not the case, and in any event, dermal fibroblasts were shown to be capable of treating a tendon injury in the prior art, as shown by the Liu article. (EX1205, 783.)

59. Beyond that, it was known that scaffolds for tissue repair strengthen over time and assume the characteristics of the native tissue as the scaffolds are replaced by native tissue. (*E.g.*, EX1205, Table 2.) Indeed, the whole point of an injury repair scaffold is for cells to use it as a scaffold to grow into functional tissue. (*E.g.*, EX1011, [0045] ("the seeded scaffold is then implanted in the body of the recipient subject, where the organized cell populations facilitate the formation

of functional tissue structures.”); EX1018, [0005] (“Described herein are novel 3-dimensional porous scaffolds ***intended for tissue regeneration*** or tissue repair.”) (emphasis added).) Further, after scaffolds are surgically implanted, it is routine for the affected part of the body to be immobilized, which gives the scaffold time to strengthen and mature into healthy tissue.

C. Crosslinking the Collagen Fibers Would Have Been Obvious in View of Huang2 or Kuo

60. Dr. Mikos also argues that the crosslinking element is not within the prior art because Huang2 does not actually crosslink its fibers, and doing so, according to Dr. Mikos, would have disadvantages, especially because the fibers are made of a PCL/collagen blend. (EX2015, ¶¶63-71.)

61. But the ’227 patent itself teaches that chemical crosslinking was a “conventional” technique within the abilities of a POSA, and specifically mentions “glutaraldehyde” and “EDC” as representative chemical agents. (EX1001, 12:49-63). Lee and Meinel (which is incorporated into Kuo) specifically disclose glutaraldehyde (EX1011, [0063]) and EDC (EX1023, 380 (incorporated in its entirety into EX1018 at [0040])) as conventional crosslinking agents. The prior art teaches crosslinking with these agents to increase strength. Thus, in my opinion it would have been obvious to crosslink using these reagents.

62. Beyond that, there are no examples in the patent that crosslinked fibers. This further demonstrates that it was well-within the skill of a POSA to chemically crosslink fibers.

63. Consistent with the statements in the '227 patent specification that chemical crosslinking was a conventional technique, Huang² teaches crosslinking as one method to improve stability of its scaffold. Likewise, Lee, as mentioned above, used glutaraldehyde to crosslink blended PCL/Collagen fibers “to increase stability and strength of the collagen.” (EX1011, [0063]; EX1220, 186:22-188:10.) Kuo also incorporates Meinel, which crosslinked collagen fibers with EDC to avoid degradation. (EX1023, 380 (incorporated in its entirety into EX1018 at [0040]).) And the literature Dr. Mikos cites also discuss crosslinking multiple implants comprising PCL. (EX2018, 1230, 1240, 1243.) In my opinion, chemical crosslinking would have been a “conventional” obvious technique.

64. In opposition, Dr. Mikos cites one of my papers and certain deposition testimony to argue that a POSA would not crosslink because of potential disadvantages, including “cytotoxic” effects. (EX2015, ¶68.) But Dr. Mikos misunderstands the point of my paper. (EX2020, 1603.) My paper, which is in the prior art, teaches the advantages of crosslinking, stating that “cross-linking is a necessity in order to maintain the structural integrity of the scaffold,” thus plainly showing that a POSA would have been motivated to crosslink collagen fibers. (*Id.*,

1594.) Indeed, the paper refers to glutaraldehyde as “the most commonly used and accepted agent for the cross-linking of biological tissues.” (*Id.*) My paper proposes different ways to improve crosslinking by suggesting chemical agents, such as EDC, that might work better than glutaraldehyde because of potential cytotoxicity concerns. Indeed, EDC was the agent described in Meinel. (*Id.*, 1593; EX1023, 380 (incorporated in its entirety into EX1018 at [0040]).) Moreover, I testified at my deposition that a POSA knows how to mitigate cytotoxicity concerns. (EX2017, 189:2-8.)

D. Dependent Claims 2-6 Would Have Been Obvious

65. Claim 2 requires the scaffold to be “one or more elongated sheets.” (EX1001, cl. 2.) Dr. Mikos argues that Kuo only teaches a rolled scaffold and thus does not teach the use of a “sheet.” (EX2015, ¶146). I disagree. To begin, the first step in Kuo’s preferred embodiment is to start with a flat “sheet.” (EX1018, Fig. 1, cl. 1; EX1220, 161:12-162:14.) Then, cells are implanted and grown on the flat sheet scaffold. (EX1018, Fig. 1, cl.1; EX1220, 161:12-162:14.) Next, the sheet is rolled, which is the fifth step in the schematic set forth as Kuo Fig. 1. (EX1018, Fig. 1, cl. 1; EX1220, 160:5-15.) Second, Dr. Mikos is not correct to the extent he is arguing that a rolled sheet is no longer a “sheet.” (EX2015, ¶146.) In my opinion, a POSA would understand that a rolled sheet is a sheet. Indeed, even the specification of the ’227 patent discloses “folding or rolling the sheet.” (EX1001,

8:40-43.) Third, a rolled scaffold is only one embodiment in Kuo. Kuo teaches that the scaffold may in the shape of either “films” or “sheets.” (EX1018, [0024].) In my opinion, that further renders the claim obvious.

66. Claim 3 requires the scaffold to be a composite of “one or more sheets.” (EX1001, cl. 3.) Kuo teaches that one embodiment for the scaffold’s shape can be “sheets.” (EX1018, [0024].) In fact, Kuo teaches using several of the rolled sheets to form a whole macroscopic tissue construct. (*Id.*, [0029].)

67. Dr. Mikos further argues that there would have been no motivation to use multiple sheets. (EX2015, ¶¶149-50.) But Dr. Mikos argues that a POSA would have wanted to enhance the mechanical properties of the scaffold to treat tendon and ligament (*Id.*, ¶130), and it was well known that multiple sheets would do that. Dr. Mikos testified and wrote in his papers that there are further advantages to having scaffolds with multiple layers. (EX1220, 146:14-22, 148:20-150:12; EX1209,1206.) I agree.

68. Claims 4, 5, and 6 require treating nerve, ligament, and tendon, respectively. As discussed in my original declaration and above (EX1003, ¶¶94-103, 129-36, 148-62; *supra* §II.B), a POSA would have been motivated to combine Huang2 and Kuo and treat those tissues.

III. LEE ALONE OR IN COMBINATION WITH KUO RENDER CLAIMS 1-6 OBVIOUS

A. Claim 1 Would Have Been Obvious

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

69. 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.B.1.c., ¶176 (emphasis added).) Ayres 2008, incorporated into the ’227 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).)

70. 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).”))

71. 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, ¶¶ 176-80, 186.) I also provided FFT testing that further confirmed that the fibers are aligned that are consistent with Lee's results. (*Id.*, ¶¶181-85.) And Dr. Mikos does not challenge that Lee obtained highly aligned collagen blended fibers. (EX2015, ¶158 ("Lee does not express any doubt regarding the alignment of its fibers."); EX1220, 192:6-15.)

72. 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, ¶185.) Thus, Lee discloses the FFT element of the claims.

2. 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

73. 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, ¶158.) 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.) 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. 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.)

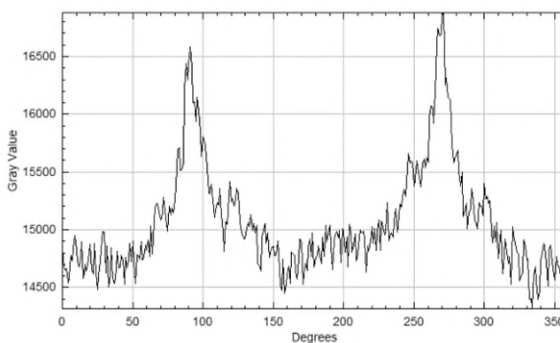
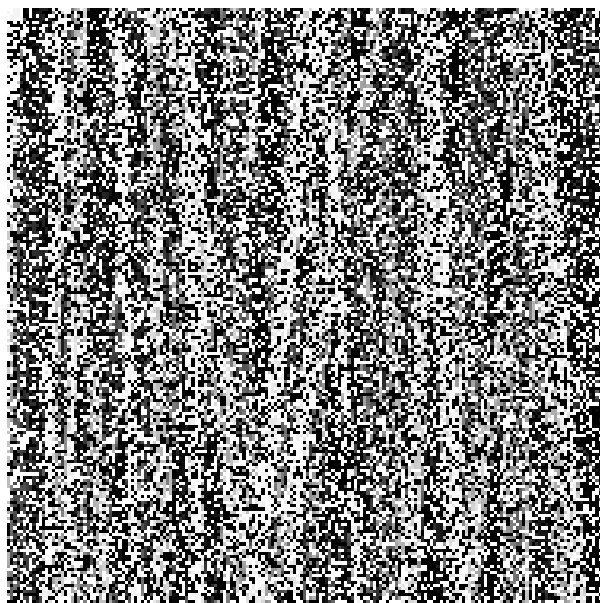
3. Dr. Mikos's Criticisms of the FFT Testing of Lee in My Original Declaration Lack Merit

74. 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, ¶¶159-74); *supra* § II.A.) Dr. Mikos's main challenge seems to be that the image that was analyzed is too low quality (EX2015, ¶165) so it is "unsuitable for analysis," but as mentioned above, I conducted additional experiments showing

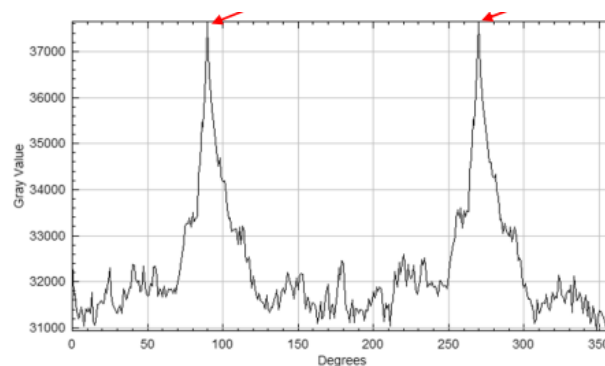
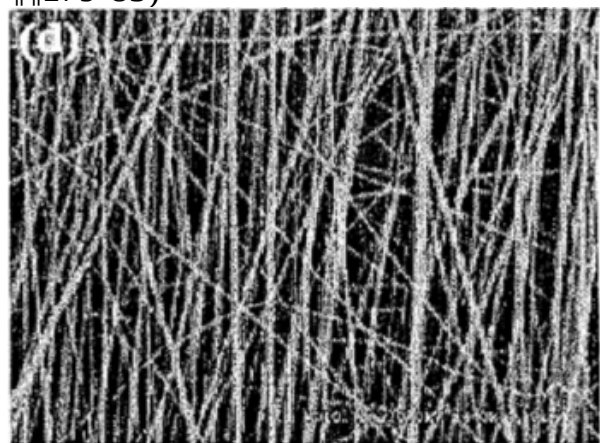
that large amounts of noise do not stop an FFT from demonstrating the claimed FFT peaks if the fibers are in fact aligned. (*Supra* §II.A.) The results demonstrate that a considerable amount of noise does not alter the presence of two alignment peaks.

75. 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 and its FFT alignment plot.

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, ¶¶179-85)



(EX1003, ¶179)

(EX1003, ¶183)

4. A POSA Would Have Been Motivated to Use Lee's Scaffold to Treat a Tendon, Ligament, or Nerve

76. Dr. Mikos incorrectly argues that a POSA would not have been motivated to use Lee's muscle scaffold to treat tendon, ligament, or nerve because the tissues are different. (EX2015, ¶¶183-99.) But the evidence identified in my original declaration (EX1003, ¶¶188-98) and above demonstrates that a POSA would have been motivated to use Lee's scaffold to treat a tendon, ligament, or nerve.

77. Indeed, as noted by the Board, "Kuo specifically discloses that its scaffolds can be used to treat muscle injuries, which is also the focus of Lee. Given that these references teach at least one common tissue that can be treated with aligned scaffolds disclosed therein . . . a POSITA would also be motivated to utilized the aligned scaffolds taught in Lee to treat the other types of tissues identified in Kuo." (Paper 13, 40.)

78. Moreover, as discussed above with regards to Huang², a POSA would have been motivated to use the scaffold made by Lee of aligned collagen fibers as the first step in the figure 1 schematic of Kuo. Lee's scaffolds are made without cells (EX1011, [0063]) and cells "may" be added (*id.*, Abstract). In fact, Lee teaches "methods of forming a biodegradable scaffold" without cells. (*Id.*, [0006].)

79. As discussed above, a Kuo teaches that “[s]caffolds for use in the instant invention may be any structural format” and that “[m]ethods of forming these various formats . . . are known to skilled artisans.” (EX1018, [0040].) Further, Kuo points to electrospun fibers for “cell growth” and “tissue engineering.” (*Id.*, [0046].) Lee teaches a scaffold that can be used for cell growth (EX1011, [0073]-[0074]) and tissue engineering (*id.*, [0002] (“The present invention is in the field of tissue engineering.”)). Thus, a POSA following Kuo would have searched for an aligned scaffold and found Lee. Indeed, both teach the use of aligned PCL/collagen scaffolds. (*Id.*, [0063], [0081]; EX1018, [0113]-[0114].) But Kuo does not experimentally verify alignment, whereas Lee does (EX1003, ¶¶176-80).

80. As taught by Kuo, a POSA would then seed the scaffold with the cells “corresponding” to the tissue it seeks to treat and then roll the scaffold to mimic the structure of the tissue. (EX1018, Abstract, [0005], [0020]-[0022], Fig. 1, [0058]; *see* EX1003, ¶¶72, 207.) The fact that Kuo discloses rolling a scaffold demonstrates that Dr. Mikos’s criticisms about a POSA not rolling the scaffold are flawed. (EX2015, ¶¶178-82.)

81. Further, I disagree with Dr. Mikos’s criticisms about elastic modulus, stiffness, and degradation rate (*id.*, ¶¶183-89) for the same reasons as discussed above, which I incorporate here. (*Supra* §II.B.3.) Indeed, the ’227 patent is

completely silent as to these aspects and Lee teaches that “[t]he use of synthetic polymers gives the ability to control scaffold rigidity and degradation rate.” (EX1011, [0050]; *see also id.*, [0092].) And it was known that scaffolds for tissue repair strengthen over time and assume the characteristics of the native tissue as the scaffolds are replaced by native tissue. (*E.g.*, EX1205, Table 2.)

B. Dependent Claims 2-6 Would Have Been Obvious

82. Claim 2 requires the scaffold in the form of one or more elongated sheets. (EX1001, cl. 2.) My original declaration explains that Lee’s electrospun fibers would constitute a sheet. (EX1003, ¶209.) Dr. Mikos does not dispute that. (*See* EX2015, ¶¶201-04.) Kuo also discloses this limitation, as discussed above. (*Supra* §II.D.)

83. Claim 3 requires that the scaffold is a composite of one or more sheets. (EX1001, cl. 3.) My opening declaration explains that Lee discloses this limitation by disclosing “a polymeric matrix can be attached to one or more polymeric matrixes to form a multilayer polymeric matrix structure.” (EX1003, ¶208.) Dr. Mikos does not dispute this. And Dr. Mikos’s arguments concerning Kuo are incorrect for the reasons set forth above. (*Supra* §II.D.)

84. Claims 4, 5, and 6 require treating nerve, ligament, and tendon, respectively. As discussed in my original declaration and above (EX1003, ¶¶188-

98, 211-29; *supra* §III.A.4), a POSA would have been motivated to treat these tissues with Lee's scaffold in view of Lee alone or Lee in view of Kuo.

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. 11,318,227 to Francis et al. (“the ’227 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”)
1015	Jose et al, <i>Fabrication and Characterization of Aligned Nanofibrous PLGA/Collagen Blends as Bone Tissue Scaffolds</i> , 50 Polymer 3778-85 (2009) (“Jose”)
1016	Fu et al, <i>Spatial Arrangement of Polycaprolactone/Collagen Nanofiber Scaffolds Regulates the Wound Healing Related Behaviors of Human Adipose Stromal Cells</i> , 18(5) Tissue Engineering, 631-42 (2012) (“Fu”)

1018	Kuo et al., U.S. Patent Application No. US 2011/0293685 A1, Pub. Date Dec. 1, 2011 (“Kuo”)
1019	Beachley et al, <i>Highly Aligned Polymer Nanofiber Structures: Fabrication and Applications in Tissue Engineering</i> (2011) in Vol. 246 Biomedical Applications of Polymeric Nanofibers (Jayakumar & Nair eds. 2011)
1020	Declaration of Emma Xu
1021	U.S. Provisional Patent App. No. 61/0255,35 (“Lee Provisional”)
1022	McClure et al, <i>Tri-Layered Vascular Grafts Composed of Polycaprolactone, Elastin, Collagen, and Silk: Optimization of Graft Properties</i> , 10 J. Mechanical Behavior Biomedical Materials 48 (2012)
1023	Meinel et al, <i>Engineering Cartilage-Like Tissue Using Human Mesenchymal Stem Cells and Silk Protein Scaffolds</i> , 88(3) Biotechnology Bioengineering 379 (2004)
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)
1204	Dilorio et al, <i>Understanding Tendon Fibroblast Biology and Heterogeneity</i> , 12(4) Biomedicines 859 (2024)
1205	Liu et al, <i>Repair of Tendon Defect with Dermal Fibroblast Engineered Tendon in a Porcine Model</i> , 12(4) Tissue Engineering 775 (2206)
1206	Clarke et al, <i>Skin-Derived Tenocyte-like Cells for the Treatment of Patellar Tendinopathy</i> , 39(3) The American J. of Sports Med. 614 (2010)
1207	Eijk et al, <i>Tissue Engineering of Ligaments: A Comparison of Bone Marrow Stromal Cells, Anterior Cruciate Ligament, and Skin Fibroblasts as Cell Source</i> , 10(5-6) Tissue Engineering 893 (2004)
1209	Pham et al, <i>Electrospinning of Polymeric Nanofibers for Tissue Engineering Applications: A Review</i> , 12(5) Tissue Engineering 1197 (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)