

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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**AVITA MEDICAL LIMITED,**  
Petitioner,

v.

**RENOVACARE SCIENCES CORP.,**  
Patent Owner

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**Case IPR2017-01243**  
**Patent 9,610,430 B2**

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**DECLARATION OF DR. GARY D. SHIPLEY**

AVITA MEDICAL VS. RENOVACARE SCI.  
IPR2017-01243

RENOVACARE EX. 2001

I, Dr. Gary D. Shipley, declare as follows:

## **I. Introduction**

1. I have been retained by Renovacare Sciences Corp. (“Patent Owner”) to serve as an expert in the above-captioned *inter partes* review proceeding (“the IPR Proceeding”) relating to U.S. Patent No. 9,610,430 (“the ’430 patent”). I have been asked to render opinions in this Declaration regarding the arguments and positions set forth in the Petition For Inter Partes Review (“the IPR Petition”) and related documentation of the IPR Proceeding.

2. I am being compensated at a rate of \$250 per hour, plus reasonable expenses incurred for my work in this matter. My compensation is not contingent on the outcome of the matter nor do I have an interest in any party to this proceeding.

## **II. Qualifications And Overview**

3. I am presently an independent consultant, and have been a consultant since July of 2010 performing work for several companies. Prior to being an independent consultant, I was a Director of Research and Development of Invitrogen Corp./Life Technologies from April, 2007 until June, 2010. Prior to that position I was the President and co-founder of Cascade Biologics, Inc. from

1992 until March 2007. I have also held academic positions. I was an Associate Professor in the Department of Cell Biology and Anatomy, Oregon Health Sciences University from 1991 to 1994. I was also an Assistant Professor there from 1985-1991. I was a Postdoctoral Fellow at the Mayo Graduate School from 1982 to 1984 and an Assistant Professor of Cell Biology at the Mayo Medical School in 1985.

4. I have a Ph.D. in Molecular, Cellular and Developmental Biology from the University of Colorado, Boulder and a bachelors degree in Microbiology from Miami University.

5. My areas of expertise include the growth and differentiation of cells in culture (in vitro), cell isolation from human and other tissues, and development and manufacture of cell growth media including defined and serum-free media for human skin cells. I do not have a degree in mechanical engineering, but I have substantial experience with laboratory equipment, including equipment for maintaining and growing cells. Such equipment involves fluid handling methods and apparatus, and so I am familiar with the subject matter of the '430 patent and the references involved in this IPR proceeding.

6. I have been informed that a person of ordinary skill in the art ("POSA") is a hypothetical person who is knowledgeable of the relevant art at the time of the invention. In my opinion a person of ordinary skill at the time of the

inventions of the '430 patent would have an advanced degree in cellular biology or biomedicine and about 5 years of experience with the isolation of cells from human tissue, and familiarity with the technologies used for wound care. Although I am not a medical doctor,<sup>1</sup> I have a doctorate in molecular, cellular and developmental biology. For over a decade I held teaching positions at the Mayo Medical School, the Mayo Graduate School, and Oregon Health Sciences University. I have over 25 years of experience in the life sciences industry relating to cell cultures, cell isolation from human and animal tissues, growth of human and animal cells in vitro, and the development of nutrient growth media to support the growth of these cells. I started a company specializing in the isolation of cells from human tissues and their in vitro expansion and cryopreservation. Therefore, I believe I would qualify as a person of ordinary skill in the art for the subject matter of the '430 patent.

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<sup>1</sup> Under the definition provided by Petitioner's expert, Dr. Shupp, a POSA would be a medical doctor specializing in skin injury, skin grafting and wound care. (Ex. 1007 at ¶ 24.) I do not believe it is necessary to be a medical doctor in order to be a POSA for the subject matter of the '430 patent, so I do not agree with Dr. Shupp's definition.

7. A copy of my resume setting forth my academic and professional credentials is submitted as Exhibit 2002.

8. To familiarize myself with the matters raised in Petitioner's IPR Petition, I have reviewed the following documents:

Exhibit No.	Description
	Petition for Inter Partes Review
1001	U.S. Patent No. 9,610,430 (“the ‘430 patent”)
1002	U.S. Patent Application Publication No. 2002/0106353 to Wood et al. (“Wood”) published August 8, 2002
1003	Navarro et al., <i>Sprayed Keratinocyte Suspensions Accelerate Epidermal Coverage in a Porcine Microwound Model</i> , Journal of Burn Care & Rehabilitation, November/December 2000, 21(6):513-518 (“Navarro”)
1004	U.S. Patent Application Publication No. 2004/0219133 to Lyles (“Lyles”) published November 4, 2004
1005	U.S. Patent No. 7,833,522 to Dixon (“Dixon”)
1006	U.S. Patent No. 6,479,052 to Marshall (“Marshall”) issued November 12, 2002
1007	Declaration of Dr. Jeffrey W. Shupp (“Shupp Decl.”)
1008	<i>Curriculum Vitae</i> of Dr. Jeffrey W. Shupp
1009	File History of the ‘430 patent (excluding non-patent literature and foreign references)
1010	Lawlor et al., <i>Dermal Contributions to Human Interfollicular Epidermal Architecture and Self-Renewal</i> , International Journal of Molecular Science, 2015, 16, 28098–28107.
1011	Stedman’s Medical Dictionary, <i>ex vivo</i> definition, <a href="http://www.stedmanonline.com/popup.aspx?aid=5188026">http://www.stedmanonline.com/popup.aspx?aid=5188026</a>
1012	Stedman’s Medical Dictionary, <i>in vitro</i> definition, <a href="http://www.stedmanonline.com/popup.aspx?aid=5200863">http://www.stedmanonline.com/popup.aspx?aid=5200863</a>
1013	<a href="https://en.wikipedia.org/wiki/Human_skin">https://en.wikipedia.org/wiki/Human_skin</a> article
1014	<a href="https://en.wikipedia.org/wiki/Nozzle">https://en.wikipedia.org/wiki/Nozzle</a> article
1015	<a href="https://en.wikipedia.org/wiki/Airbrush">https://en.wikipedia.org/wiki/Airbrush</a> article
1016	US Provisional Application No. 60/705,906 filed August 5, 2005

9. I have been asked by the Patent Owner's attorneys to address whether any of the grounds based on: (1) Wood; (2) Wood and Navarro; (3) Wood and Lyles; (4) Wood and Dixon; or (5) Wood and Marshall, as proposed by the Petitioner and Dr. Shupp, disclose

- *providing a single cell-suspension of cells comprising progenitor skin cells in a serum-free physiological solution in a sterilizable container, wherein the cells are obtained from the subject's normal skin tissue that has been treated with enzymes so as to release the cells from the dermal-epithelial cell junction, wherein the skin cells have not been subjected to ex vivo or in vitro expansion;*
- *contacting the single-cell suspension of cells with a gas flow at an outlet of the container to create droplets of the suspension at a flow-controlled spray head; and*
- *spraying the droplets onto the wounded area of skin without forming a closed cell sheet so that the single cells are distributed directly and evenly and the cells regenerate normal skin by in situ multiplication to heal the wounded area in the absence of applying a preformed skin graft,*

within the meaning of the claims of the '430 patent.

10. I do not claim to be an expert in patent law or the legal intricacies of construing patent claims. For purposes of this Declaration, I used the plain and ordinary meaning of the '430 patent claim language I was asked to consider unless that meaning was inconsistent with the '430 patent specification.

11. For the reasons explained in this Declaration, I conclude that: (1) Wood; (2) Wood and Navarro; (3) Wood and Lyles; (4) Wood and Dixon; and (5) Wood and Marshall, as proposed by the Petitioner and Dr. Shupp, do not disclose:

- *providing a single cell-suspension of cells comprising progenitor skin cells in a serum-free physiological solution in a sterilizable container, wherein the cells are obtained from the subject's normal skin tissue that has been treated with enzymes so as to release the cells from the dermal-epithelial cell junction, wherein the skin cells have not been subjected to ex vivo or in vitro expansion;*
- *contacting the single-cell suspension of cells with a gas flow at an outlet of the container to create droplets of the suspension at a flow-controlled spray head*"; and
- *"spraying the droplets onto the wounded area of skin without forming a closed cell sheet so that the single cells are distributed directly and evenly and the cells regenerate normal skin by in situ multiplication to heal the wounded area in the absence of applying a preformed skin graft,*

within the meaning of the claims of the '430 patent.

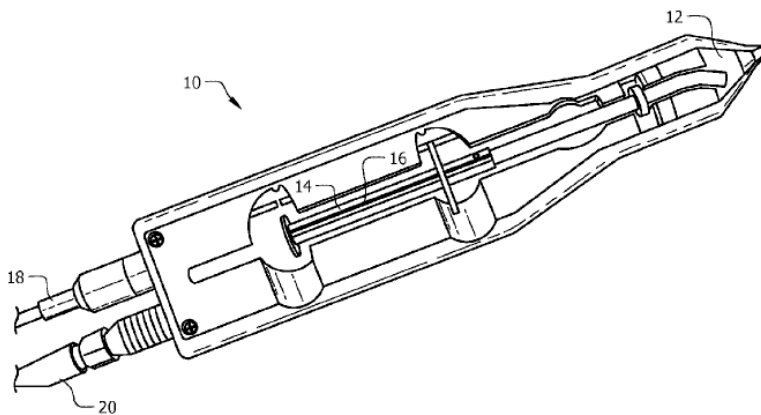
### **III. '430 Patent**

12. The '430 patent discloses a cell spraying device, method and sprayed cell suspension. (Ex. 1001, p. 1.) In various embodiments, a device and method is provided for spraying a cell suspension through a controlled spray head suitable for application to a patient utilizing a spray device. In various embodiments an electronically controlled apparatus is provided as a medical device for distribution



of tissue regenerating cells in a sterile suspension over a tissue surface via electronic controlled compressed gas and/or pump driven spraying through a sterilizeable spray head. In various embodiments the apparatus is capable of providing continuous force application in a single shot and generating suspension drops containing cells. In various embodiments, the apparatus may provide means to measure and control parameters such as flow, pressure, and/or temperature. (Ex. 1001 at 3:16-33 and 7:25-47.)

13. FIG. 1 of Ex. 1001 shows an embodiment of a spray gun having a controlled spray head:



14. The apparatus may comprise a first member, not shown, and second member **10** wherein: the first member includes power supply, gas/air supply and electronic controls, and the second member **10** includes a sterilizeable spray head **12** and a container **14** with the cell suspension **16**. In that case both members may be connected through connectors **18, 20**. One connector may supply power and the other connector may supply gas/air from the power supply and gas/air supply

within the first member, not shown, respectively. The suspension is transformed into small airborne droplets by mixing the suspension with air/gas within the second member **10** when the container **14** is actuated to release the solution **16**. (Ex. 1001 at 7:60-8:10.)

15. The '430 patent also discloses providing a cell suspension, where the cells in the suspension are preferably autologous cells or stem cells obtained by subjecting a tissue sample including cells suitable for grafting to a patient, to at least a physical and/or chemical dissociating means capable of dissociating cells in the tissue sample; taking the cells suitable for grafting on to a patient into a saline solution, and removing large cellular conglomerates to produce a cell suspension. (Ex. 1001 at 3:16-33.)

16. The '430 patent discloses the importance of controlling the spray of the cell suspension to achieve an even cell distribution over the region to be treated. (Ex. 1001, 6:58-59: "An important advantage of the invention is an even cell distribution.") It distinguishes uncontrolled hand driven sprays from the present controlled spray of the suspension because uncontrolled sprays result in an uneven cell distribution. Such uncontrolled sprays include those disclosed in Navarro et al. (2000) (Ex. 1003), the disadvantages of which were discussed in the Background of the Invention of the '430 patent. (Ex. 1001 2:30-42.) The primary reference in the Petition, Wood (Ex. 1002), also discusses uncontrolled hand

driven sprays using, for example, a syringe and needle. (Ex. 1002, ¶¶ [0065], [0092], [0097], and [0112].)

17. Claim 1 of the '430 patent reads as follows:

*1. A method to treat a wounded area of skin on a human subject, comprising:*  
*providing a single cell-suspension of cells comprising progenitor skin cells in a serum-free physiological solution in a sterilizable container, wherein the cells are obtained from the subject's normal skin tissue that has been treated with enzymes so as to release the cells from the dermal-epithelial cell junction, wherein the skin cells have not been subjected to ex vivo or in vitro expansion;*  
*contacting the single-cell suspension of cells with a gas flow at an outlet of the container to create droplets of the suspension at a flow-controlled spray head; and*  
*spraying the droplets onto the wounded area of skin without forming a closed cell sheet so that the single cells are distributed directly and evenly and the cells regenerate normal skin by in situ multiplication to heal the wounded area in the absence of applying a preformed skin graft.*

#### **IV. Claim Constructions**

18. I have read the Petitioner's and Dr. Shupp's claim constructions. I do not claim to be an expert in patent law or the legal intricacies of construing patent claims, but I believe some of these claim constructions are inaccurate or

misleading. The following claim constructions are addressed to clarify them; however, I reserve the right to further address claim constructions upon additional reflection and study of the documents in this proceeding:

**A. “*single cell-suspension*” or “*single-cell suspension*”**

19. Dr. Shupp interprets “single cell-suspension” or “single-cell suspension” as “a suspension comprising individual cells that are not adhered to, or otherwise associated with, each other.” (See Ex. 1007, ¶¶ 39-43, and in particular ¶¶ 42 and 43.) I find his definition misleading because it would technically include any suspension that included individual cells, and I don’t believe a POSA would understand a “single cell suspension” to be defined that broadly. Under Dr. Shupp’s definition, a suspension could include a very high percentage of large conglomerates of cells and would still fall within his definition provided the suspension included at least a few individual cells.<sup>2</sup> A POSA would not call such a

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<sup>2</sup> In fact, in ¶ 43 Dr. Shupp states: “Consistent with dependent claims 6 and 7, this construction does not preclude the presence of some amount of agglomerated cells in the suspension, so long as there are also individual cells present.” (Ex. 1007, ¶43, underlining added.) His definition does not rule out the case when most of the cells are agglomerated, which a POSA would not call a “single cell suspension.”

suspension a “single-cell suspension” nor would that be the single-cell suspension used in the ’430 patent. In my opinion Dr. Shupp’s definition is unreasonably broad because it gives no sense of the composition of individual cells to ones that are not individual cells. In my opinion, a POSA would understand that a single-cell suspension would be a suspension of cells that included primarily single cells but may include a minor percentage of small conglomerates of cells, and may include relatively few or no large conglomerates of cells.

20. Dr. Shupp’s definition is also incomplete because it fails to mention a necessary element of the suspension for the purposes of the ’430 patent: cell viability. Therefore, Dr. Shupp’s definition would improperly include a suspension of individual, dead cells—which would never work for the purposes of the ’430 patent. Indeed, Dr. Shupp recognizes the need for viability of cells in the suspension when discussing cell morphology in paragraphs 60 and 61 of his Declaration. (See Ex. 1007, ¶¶ 60-61, referencing viability of cells in the suspension.)

21. A POSA would define a “single-cell suspension” to include a suspension of viable cells that includes primarily single cells or small conglomerates of cells, and which includes relatively few or no large conglomerates of cells.

**B. “a gas flow”**

22. Dr. Shupp relates “a gas flow” to “the flow of a propellant gas that forces the suspension through a flow-controlled spray head.” (Ex. 1007, ¶ 49.) Dr. Shupp’s characterization attempts to import additional aspects into “a gas flow” such as “propellant gas,” “forcing the suspension” and “through a flow-controlled spray head.” A POSA would not need to specially interpret “a gas flow” and would not associate “propellant gas,” “forcing the suspension,” and “through a flow-controlled spray head” with an interpretation of “a gas flow.”

23. Dr. Shupp’s characterization does not accurately represent the teaching of “a gas flow” in the specification of the ’430 patent. For example, Dr. Shupp attempts to relate “a gas flow” to “a flow-controlled spray head,” citing Col. 7, lns. 34-36. However, that excerpt from the ’430 patent does not use the term “flow-controlled spray head,” nor does it reference flow control. It merely states: “In this embodiment, the apparatus can be operated by producing a gas flow, for example air from a compressor, to engage the spray head, [ ].” (Ex. 1001, 7:34-36; underlining.) The excerpt refers to a “spray head” – it does not refer to a “flow-controlled spray head.” Flow control may be performed by different components of the embodiments of the ’430 patent, as discussed in the following paragraph.

24. A POSA would understand that the ’430 patent allows for gas flow to be controlled by various components in various locations of the apparatus of the

'430 patent, in various embodiments. For example, the '430 patent states: “[a]n embodiment of the spray gun includes an electronically controlled apparatus used as a medical device to operate the spraying through a sterilizeable spray head. (Ex. 1001, 7:25-27.) It goes on to state: “The apparatus may provide means to measure and control parameters such as flow, pressure, and/or temperature.” (Ex. 1001, 7:46-47; underlining added.) An example of the spray gun is shown in FIG. 1; however, the '430 specification makes it clear that the apparatus of FIG. 1 may comprise a first member (not shown) and a second member (10) wherein the first member includes “power supply, gas/air supply and electronic controls.” (Ex. 1001, 7:60-67; underlining added.) The first member and the second member can be connected through connectors 18 and 20. (Ex. 1001, 7:65-66.) And the first and second member can include “sensor/effector controls in the first and second member.” (Ex. 1001, 8:11-14; underlining added.) The '430 patent also discloses an embodiment which is an “all-in-one device for hand-held operation.” (Ex. 1001, 8:15-18.) Therefore, a POSA would understand that “a gas flow” can be controlled in various components of various embodiments of the '430 patent.

25. Consequently, a POSA would find Dr. Shupp’s characterization of “a gas flow” is not accurate, not consistent with the '430 patent, and not necessary.

**C. “*ex vivo* or *in vitro* expansion” and “*wherein the skin cells have not been subjected to ex vivo or in vitro expansion*”**

26. Dr. Shupp asserts that “*ex vivo* or *in vitro* expansion” would be understood by a POSA to mean “the multiplication of cells occurring outside of the human body or in an artificial environment.” (Ex. 1007, ¶¶ 46-48.) It is more helpful to understand the claims by interpreting the entire phrase “wherein the skin cells have not been subjected to *ex vivo* or *in vitro* expansion.” For example, a POSA would understand that some minor expansion of the cell population may occur during the process of cell isolation and while the cells are in suspension before being applied to a patient. For example, cells that were in the G2 phase or M phase of the cell cycle at the time they were isolated from the tissue may continue to complete the cell cycle and undergo mitosis while they are held in the serum-free nutrient solution provided and especially if the suspension of cells is held at 37°C. Thus, a minor amount of multiplication may be expected. However, in the absence of certain hormones or other molecules, cell growth is not promoted by the nutrient solution. That is, cells in G1 phase that have not committed to S phase of the cell cycle are not placed in an environment that promotes the proliferation of the cells. Therefore, a POSA would understand cells in suspension which “have not been subjected to *ex vivo* or *in vitro* expansion” are cell suspensions where some minor multiplication of cells outside of the human body



or in an artificial environment may occur, but such cell multiplication is not promoted.

**D. “*flow-controlled spray head*”**

27. Dr. Shupp asserts that the term “flow-controlled spray head” “has a plain and ordinary meaning as would be understood by a POSA, and refers to a spray device which controls or regulates the flow of a fluid therethrough.” (Ex. 1007, ¶ 50.) Dr. Shupp then states “[t]he term [“flow-controlled spray head”] would include, for example, a ‘nozzle.’” Because Dr. Shupp employs the phrase “would include”, it is not entirely clear what he is asserting. If he is asserting that a nozzle, by itself, is one example of a “flow-controlled spray head,” a POSA would disagree with his interpretation based on reading and understanding the ’430 patent.

28. A POSA would understand that a nozzle receiving an unpressurized, weak, or highly varied stream of fluid may not control the fluid passing through it—in such cases the fluid source will control or regulate the flow of fluid. A POSA would also understand the same is true for a nozzle with an aperture that is large with respect to the volume of fluid being transferred. Thus, a POSA would understand that a spray head and the means for providing and controlling the fluid to the spray head must be considered together to determine if the system provides a “flow-controlled spray head.” The ’430 patent describes various means for

controlling fluid which Dr. Shupp's example does not include, some of which are discussed in the following paragraphs.

29. Dr. Shupp asserts that the specification of the '430 patent supports his assertion, and cites an excerpt from the disclosure: "[the] invention also contemplates an apparatus containing a spray head to distribute the cells. The suspension may be sprayed through *any type of nozzle* that transforms liquid into small airborne droplets." (Ex. 1007, ¶ 51, citing Col. 7, lns. 21-24 of the '430 patent [Ex. 1001].) However, the excerpt references a "spray head," and not a "flow-controlled spray head." A POSA would understand that, as described above, the use of a nozzle does not in itself provide a flow-controlled spray head. The reference to Col. 7, lns. 21-24 of the '430 patent is consistent with my interpretation, because the excerpt does not say that any type of nozzle can be used. It states that any type of nozzle that transforms liquid into small airborne droplets can be used. A POSA would understand the configuration of the means for controlling fluid to the nozzle with the nozzle determine if liquid is transformed into small airborne droplets. Thus , they work in conjunction and droplets will not come from just any nozzle.

30. To address a flow-controlled spray head, the '430 patent provides embodiments that can control the flow rate and pressure of a gas used to create droplets of the suspension at the flow-controlled spray head, such as the

electronically controlled examples discussed in Paragraph 24, above. In conjunction with these control examples, the '430 patent states:

“The suspension is transformed into small airborne droplets by mixing the suspension with air/gas within the second member **10** when the container **14** is actuated to release the solution **16**. The apparatus may comprise a first and second member wherein both members are wirelessly connected for data exchange . . . to connect sensor/effector controls in the first and second member.”

(Ex. 1001, 8:7-14.) Therefore, the flow-controls exemplified by embodiments of the '430 patent can be distributed over the device and are more than a nozzle.

31. Therefore, Dr. Shupp's characterization of a nozzle itself being a “flow-controlled spray head” as understood from the '430 patent is inaccurate and an oversimplification of the term.

**E. “*closed cell sheet*”**

32. Dr. Shupp states that “closed cell sheet” would be understood by a POSA to refer to a collection of adherent cells in the form of a sheet structure.” Dr. Shupp cites Col. 4, lns. 41-44 of the '430 patent and concludes with a slightly different definition: “[a]ccordingly, a ‘closed cell sheet’ would be understood to encompass a continuous sheet of cells.” (Ex. 1007, ¶ 53.) His statements are confusing, and it is not clear which definition is intended. Regardless, a POSA would arrive at a different definition for at least the following reasons.

33. Rather than attempt to interpret “closed cell sheet” as an isolated phrase to understand its meaning, a POSA would read at least the last element of claim 1, which recites:

“spraying the droplets onto the wounded area of skin without forming a closed cell sheet so that single cells are distributed directly and evenly and the cells regenerate normal skin by in situ multiplication to heal the wounded area in the absence of applying a preformed skin graft.”

34. A POSA would understand that the “closed cell sheet” of claim 1 is set forth in the context of sprayed cells at the time they are sprayed onto an area, and not a grown sheet of cells. However, Dr. Shupp’s definitions appear to include a grown sheet of cells, and therefore are incorrect and overly broad with regard to claim 1.

35. A POSA would interpret the statement of the ’430 patent Col. 4, lns. 41-44 differently than Dr. Shupp. A POSA would understand that statement to mean the tissue required to create the suspension of the ’430 patent is a relatively small biopsy area because the suspension can be made from a relatively small number of cells, as contrasted with the number of cells needed for a grown sheet graft of the prior art that must cover the entire wound.

36. Based on the claim language and the specification of the ’430 patent, a POSA would understand that the “closed cell sheet” is an accumulation of cells

sprayed onto a wounded area of skin so that the sprayed cells form a layer of cells with a sufficient density so as to cover and coat the area with sprayed cells. The POSA would further appreciate that the sprayed cells lack the cell-to-cell junctions of a grown sheet of cells at the time of spraying.

37. Accordingly, a POSA would appreciate that “spraying the droplets onto the wounded area of skin without forming a closed cell sheet so that single cells are distributed directly and evenly and the cells regenerate normal skin” means that the cells sprayed “without forming a closed cell sheet” would be spread out evenly and not completely cover the area. Such cells could grow over time to form a new layer of skin by in situ multiplication to create a sheet of cells with cell-to-cell junctions that create new skin and heal the wound. Blister formation is avoided by the use of single cells without forming a closed sheet. (Ex. 1001, 4:33-60.)

**F. “*preformed skin graft*” and “*in the absence of applying a preformed skin graft*”**

38. Dr. Shupp interpreted “preformed skin graft” as “any skin graft, such as a split-thickness graft, full-thickness graft, mesh graft, micro-grafting, and cultured epithelial autografts, that is formed before spraying the droplets.” (Ex. 1007, ¶ 54.) Dr. Shupp does not offer a reason for why his definition requires that the skin graft is formed “before spraying the droplets.” A POSA would not

interpret the term “preformed” in “preformed skin graft” as a reference to a time of spraying the droplets. A POSA would interpret a “preformed skin graft” to be a skin graft made of tissue having formed cell-to-cell junctions and capable of substantially covering the wound. Therefore, a POSA would interpret “in the absence of applying a preformed skin graft” as recited in claim 1 as meaning the sprayed cells regenerate normal skin by in situ multiplication to heal the wound without the application of a skin graft or a cultured epithelial graft during the wound healing process.

**G. “*continuous force application*”**

39. Dr. Shupp interprets “continuous force application,” stating: “. . . the phrase may be understood to mean the application of force, manually or otherwise, continuously for about 30 seconds to about 10 minutes.” (Ex. 1007, ¶¶ 64-65.) I disagree with Dr. Shupp’s claim construction for several reasons. First, a POSA would not require a specific time range for the application of force in a “continuous force application.” Second, each time the ’430 patent specification discusses a “continuous force application” it is in the context of an automated application—not a manual application—as discussed in the following paragraphs.

40. The ’430 patent specification provides a first reference to “continuous force application” at Col. 3, lines 27-33:

“According to the invention an electronically controlled apparatus is provided as a medical device for distribution of tissue regenerating cells in a sterile suspension over a tissue surface via electronic controlled compressed gas and/or pump driven spraying through a sterilizeable spray head, providing continuous force application in a single shot and generating suspension drops containing cells.”

(Ex. 1001, 3:27-33, underlining added.) This excerpt from the specification does not specify a duration of the application, and makes it clear that the application is electronically controlled and automated.

41. A second reference to “continuous force application” is found at Col. 7, lines 34-45 of the ’430 patent specification:

“In this embodiment, the apparatus can be operated by producing a gas flow, for example air from a compressor, to engage the spray head, or forcing the cell suspension pump driven through the nozzle, for example by motor operated pushing of a sterile Luer-lock syringe containing the cell suspension, the gas may flow through a sterile syringe. An alternative is to produce the spray without mixing with gas. The apparatus also may provide continuous force application over a range of about 0.5 to about 10±1.0 minutes for a single shot, or several shots, and generate suspension drops containing cells in the range of about 30 to about 500±200 millimeters.”

(Ex. 1001, 7:34-45, underlining added.) This excerpt also emphasizes that the apparatus provides the “continuous force application” and that it is not a manual

operation. The time duration range is suggested (“may provide”), but is not mandatory.

42. Accordingly, a POSA would understand a “continuous force application” as used by the ’430 patent to be an automated and controlled force.

#### **H. Use Of Plain and Ordinary Meaning**

43. For purposes of this Declaration, I used the plain and ordinary meaning of the ’430 patent claim language I was asked to consider unless that meaning was inconsistent with the ’430 patent specification.

### **V. Petitioner’s Prior Art References**

#### **A. Dr. Shupp’s Reproduction of the Wood Method Does Not Establish A Single Cell Suspension Or Tissue Growth**

44. Dr. Shupp outlines his characterizations of Wood in paragraphs 67-83 of his Declaration; however, the results provided in his Declaration are inconclusive and do not establish a single cell suspension or tissue growth. I will detail some issues with his reproduction of the method of Wood in the following paragraphs. (Ex. 1007, ¶¶ 67-83.)

45. Dr. Shupp’s Declaration paragraphs 72-73 discuss the use of a nutrient solution and physiological saline in Wood ¶¶ [0055] and [0057]; however, Wood does not promote use of physiological saline in all method steps it outlines.



One notable example is in Example 1, provided by Wood ¶¶ [0100]-[0114]. For example, at Wood ¶ [0106], sterile water for injection (10 ml) is mixed with lyophilised trypsin to give a 0.5% trypsin enzyme solution. (Ex. 1002, ¶ [0106].) A tissue sample is incubated at 37 degrees C for 10-15 minutes in the enzyme solution. (Ex. 1002, ¶ [0108].) Thus, tissue (and cells) are exposed to a solution that is not physiological saline or nutrient solution.

46. Dr. Shupp states that Wood's use of serum-free nutrient solution such as physiological saline "is due to the elimination of ex vivo or in vitro expansion of the cells in the suspension." (Ex. 1007, ¶ 73, citing Wood, Ex. 1002, ¶ [0061].) However, a POSA would understand that xenogenic serum is a common additive in grafting culture medium and is well known to cause potential infective and hypersensitivity problems. Dr. Shupp fails to point out this reason for avoiding serum, which in my opinion is the primary reason for avoiding serum in the nutrient solution.

47. Dr. Shupp states: "A POSA would understand that a 50 µm filter size permits the passing of individual human skin cells and removes congregates of 2 or more skin cells (on average 60 µm or more in length) []." And: "[a]dditionally, a filter size of 200 µm may permit, at the cross-section, up to  $8*8=64$  cells (assuming smallest cells with a diameter of 25 µm) to pass and thus, has a cut-off of about 65-cell congregates." (Ex. 1007, ¶ 74.) However, his calculations assume that cells

are inflexible and do not conglomerate in irregular shapes. A POSA would understand that cells can fit through smaller apertures than their diameter and conglomerates will form in different shapes and therefore different sizes. Therefore, Dr. Shupp's filter cutoff calculations are not completely accurate.

48. I have reviewed Figure 1, and while it does appear to show some stained cells there is no way to determine whether the method of Wood performed by Dr. Shupp produces a single cell suspension from Figure 1. Dr. Shupp and Figure 1 do not provide any test or evidence of viability of the cells. Dr. Shupp and Figure 1 do not provide any evidence of single-cell and cell conglomerate distribution or concentration. A POSA would want to know cell viability and the nature of the single-cell and cell conglomerate distribution in order to determine if a suspension is a single-cell suspension. Therefore, it is impossible for a POSA to say from Figure 1 that the method of Wood creates a single-cell suspension. (Ex. 1007, ¶ 75.)

49. Dr. Shupp references a syringe attached to a nozzle "for spraying or dripping on to the wound area." (Ex. 1007, ¶77, citing Wood, ¶ [0112].) He relies on his definition of a "flow-controlled spray head" as being a nozzle (by his definition, which I explicitly disagree with, as discussed in the Claim Constructions section, above). Dr. Shupp also cites Wood ¶ [0064] to assert that the nozzle can be "any type of nozzle that transforms liquid into small airborne

droplets.” However, Wood ¶ [0064] fails to provide a flow-controlled spray head under the ’430 patent because a nozzle that transforms liquid into small airborne droplets is not working of its own accord, but rather as a system which relies upon a certain flow and pressure of the fluid introduced to the nozzle. Therefore, a nozzle itself is not a flow-controlled spray head within the meaning of the ’430 patent. (See the discussion of “a gas flow” and “a flow-controlled spray head”, with regard to the Claim Constructions section where I disagree with Dr. Shupp’s definitions.)

50. Dr. Shupp discusses the need for the nozzle of Wood to not significantly damage the cells and that “a POSA would understand that the cells in the suspension will have a morphology that is similar to the cells in the droplets.” (Ex. 1007, ¶ 78.) Dr. Wood provides Figure 2 as his evidence that the cells in the suspension (panel A) are similar to the morphology of the cells in the droplets (panel B). (Ex. 1007, ¶ 79.) However, a POSA would know that one cannot tell similar morphology as defined by simply comparing two 20X microscope views. There are viability tests that can be performed, such as trypan blue staining or plating efficiency. No viability test data are provided, and in my opinion a microscope slide comparison of cells before and after spraying a suspension cannot alone demonstrate viability and, therefore, meet the definition of similar

morphology. A POSA cannot draw the conclusions that Dr. Shupp is making by simply comparing these samples by light microscopy.

51. Dr. Shupp concludes that the cell suspension provided by Wood can be used for “resurfacing and regeneration of damaged tissue,” that it can be used “without applying a preformed skin graft; that is prior to spraying the droplets, no other skin graft was applied to the wound.” (Ex. 1007, ¶ 82.) Dr. Shupp also asserts that Wood can “produce a suspension of cells in a ratio to each other comparable with those seen in situ . . .” He concludes “due to the lack of ex vivo or in vitro culture expansion of the cells, such uncultured cells are present in the suspension in a ratio comparable to that found in situ in the normal skin.” (Ex. 1007, ¶ 83.) However, Dr. Shupp presents no evidence that said uncultured cells are present in the suspension in a ratio comparable to that found in situ and no evidence of healing of a wound by the method of Wood. He is merely parroting excerpts from Wood for his declaration. (Ex. 1007, ¶¶ 82-83.) Such assertions are not evidence of efficacy of Wood, nor can they be used as proof that Wood provides wound healing in the absence of applying a preformed skin graft.

52. Dr. Shupp offers no explanation for his assertion that “a POSA would at once envisage that a ‘propellant fluid’ includes a propellant gas.” (Ex. 1007, ¶ 77.) However, Dr. Shupp references “propellant gas” numerous times throughout his declaration. (Ex. 1007, ¶¶ 49, 77, 95, 96, 109, 114, 117, 120.)

53. A POSA would understand that the microscope slides offered by Dr. Shupp do not prove that Wood provides a single-cell suspension, do not prove that the morphology of the suspension is not affected by spraying, and do not prove the efficacy of the method of Wood for healing. A POSA would understand that tests could have been performed to attempt to establish these things, but were not performed by Dr. Shupp.

54. As I state with regard to Example 1 in paragraphs 65 to 70 below, it is possible that the Example 1 method of Wood would not be efficacious due to damage to the cells arising from the use of sterile water as opposed to an isotonic solution for application of trypsin to attempt to dissociate cells in the biopsy tissue. (See paragraphs 65-70, below.)

**B. Wood Does Not Teach the Elements of Claim 1**

i. Wood fails to teach “*providing a single cell-suspension of cells . . . skin tissue . . . treated with enzymes so as to release the cells from the dermal-epithelial cell junction, wherein the skin cells have not been subjected to ex vivo or in vitro expansion*”

55. Dr. Shupp relies on Wood ¶ [0020] to assert that Wood discloses “subjecting a tissue sample including cells suitable for grafting to a patient, to an enzyme suitable for dissociating cohesive pieces of the tissue stratum in the

sample.” This portion of Wood refers to the use of a single enzyme and not “enzymes,” which is plural. (Ex. 1007, ¶ 92.) Dr. Shupp also references Wood ¶ [0051] which states: “dissociation of the tissue sample is achieved by placing the sample in a pre-warmed enzyme solution containing an amount of enzyme sufficient to dissociate cellular stratum in the tissue sample.” This excerpt of Wood also refers to a single enzyme and not “enzymes.” (Ex. 1007, ¶ 92.)

56. Dr. Shupp concludes: “[t]hus, Wood discloses the limitation that the skin tissue can be ‘treated with enzymes so as to release the cells.’” Apparently, Dr. Shupp is relying upon a list of enzymes he references from Wood ¶ [0050] which lists chemical dissociation means that “might include, for example, digestion with enzymes such as trypsin, dispase, collagenase, trypsin-edta, thermolysin, pronase, hyaluronidase, elastase, papain and pancreatin.” (Ex. 1007, ¶ 92.) However, Dr. Shupp does not explain why he believes Wood teaches that multiple enzymes would be used. Dr. Shupp does not account for several references to use of a single enzyme in Wood (Ex. 1002):

- ¶[0015] references a single enzyme, and provides trypsin as an example;
- ¶[0016] refers to “enzymes” but references “enzymes like trypsin” as an example, which implies the use of a single enzyme selected from possible enzyme candidates – not the use of multiple enzymes.

- ¶[0021] references subjecting a tissue sample to an enzyme for dissociating pieces of the tissue;
- ¶[0051] references trypsin used as a single enzyme in two places, and states “any other enzyme such as dispase, collagenase, trypsin-edta, thermolysin, pronase, hyaluronidase, pancreatin, elastase, and papain that cause cells to become detached from other cells [] may be used for this purpose”, thus all references are to a single enzyme use;
- ¶[0061] references use of a single enzyme, and provides trypsin as an example;
- ¶[0081] references a container for a single enzyme;
- ¶[0085] references the enzyme reaching a desired temperature and an amount of time the enzyme has been in a solution;
- ¶[0092] references a container for a separation enzyme (singular) and a sterile solution for suspension of the enzyme;
- ¶[0094] references “lyophilized separation enzyme”;
- ¶[0106] relates to Example 1 and references “the separation enzyme (lyophilized trypsin)”; and
- ¶[0106] relates to Example 2 and references “the enzyme”.

57. In my opinion, Wood does not teach multiple enzymes are used.

When Wood uses the phrase “enzymes” it appears to do so with reference to

different enzymes that may be employed singly, but I do not see support for use of multiple of these enzymes being used. In fact, Wood appears to teach limiting exposure to enzyme to avoid decreases in viability of the cellular suspension. (See Ex. 1002, Wood, ¶¶ [0016] and [0062].) Therefore, since Dr. Shupp has not provided any factual basis for his assertion of the application of enzymes in Wood. The numerous references to a single enzyme Wood outweigh a conclusory statement by Dr. Shupp. Therefore, the Petition and Dr. Shupp do not show that Wood teaches “*skin tissue [ ] treated with enzymes,*” as recited in claim 1 of the ’430 patent.

**ii. Wood fails to teach “*contacting the single cell suspension of cells with the gas flow at an outlet of the container to create droplets of the suspension at a flow-controlled spray head*”**

58. Dr. Shupp relies on his definitions for “a gas flow” and “a flow-controlled spray head” to interpret them to refer to “a propellant gas which acts to force the suspension through a flow-controlled spray head (e.g., a nozzle)” and to conclude that Wood ¶ [0112] (Ex. 1007) teaches these elements. (See ¶ 52, above.) Dr. Shupp also references Wood ¶ [0064] for his assertion that his nozzle can be “any type of nozzle that transforms liquid into small airborne droplets.” However, Wood ¶ [0064] fails for the same reasons as provided above: a nozzle



that transforms liquid into small airborne droplets is not working of its own accord, but rather as a system which relies upon a certain flow and pressure of the fluid introduced to the nozzle. Therefore, a nozzle itself is not a “flow-controlled spray head” within the meaning of the ’430 patent. (See the discussion of “a gas flow” and “a flow-controlled spray head” in the Claim Constructions section which identify issues with Dr. Shupp’s definitions.)

59. Dr. Shupp’s claim constructions fail to account for the flow-control teachings of the ’430 patent which are referenced by the “flow-controlled” portion of “flow-controlled spray head” of claim 1. The discussion provided above concerning “a gas flow” and “a flow-controlled spray head” explains why Dr. Shupp’s reasoning is defective and how the ’430 patent supports flow-controlled fluid and spray to avoid the problems of prior art, such as Wood.

60. Wood ¶ [0112] (Ex. 1007) employs an approach that is precisely what the ’430 patent has identified as a problem in the prior art: hand driven sprays which result in an uneven cell distribution. (Ex. 1001, 2:30-47, “A hand driven spray method and subsequent distribution of the cells, however, is not performed in a controlled manner and thus results in uneven cell distribution.”) Wood ¶ [0112] teaches a nozzle attached to a syringe “for spraying or dripping on to the wound area,” and both may result due to the uneven nature of delivering fluid by hand pressure, which is also a problem that the ’430 patent invention has solved. The

'430 patent discloses the importance of controlling the spray of the cell suspension to achieve an even cell distribution over the region to be treated. (Ex. 1001, 6:58-59: "An important advantage of the invention is an even cell distribution.") It distinguishes uncontrolled hand driven sprays from the present controlled spray of the suspension because uncontrolled sprays result in an uneven cell distribution. the disadvantages of which were discussed in the Background of the Invention of the '430 patent. (Ex. 1001 2:30-42.)

61. A POSA would understand that Dr. Shupp has not shown that "any type of nozzle that transforms liquid into small airborne droplets" can be a "flow-controlled spray head" within the meaning of the '430 patent, and instead seeks to interpret the claim terms as covering the prior art hand driven approaches despite the '430 patent teachings to the contrary.

62. Dr. Shupp admits that Wood does not expressly disclose a "gas flow" at an outlet of the container to create droplets. (Ex. 1007, ¶ 95.) He asserts that Wood ¶ [0064] refers to a propellant fluid; however, he continues to fail to show that Wood teaches a "flow-controlled spray head" as provided by the '430 patent, and he fails to explain why, if any type of nozzle would work, there would be a motivation to add a gas flow at an outlet of a container to create droplets. If any type of nozzle would work, a POSA would opt for simplicity and not additional controls and hardware. Therefore, Dr. Shupp fails to state a rationale for why a

POSA would use a propellant gas to force a suspension through a nozzle. (Ex. 1007, ¶¶ 95-96.)

63. For at least these reasons the Petition and Dr. Shupp fail to show that Wood teaches “*contacting the single cell suspension of cells with the gas flow at an outlet of the container to create droplets of the suspension at a flow-controlled spray head.*”

**iii. Wood fails to teach “*spraying the droplets onto the wounded area of skin without forming a closed cell sheet so that the cells are distributed directly and evenly and the cells regenerate normal skin by in situ multiplication to heal the wounded area in the absence of applying a preformed skin graft*”**

64. Dr. Shupp asserts that “Wood discloses that the suspension is sprayed ‘directly to a region . . . in a manner that facilitates spreading of the cell suspension in a relatively even distribution over the graft region.’ See Wood, ¶ [0019].” (Ex. 1007, ¶ 99.) However, Wood ¶ [0019] does not use the term “sprayed.” Instead, it reads: “[0019] (b) administering the suspension directly to a region on the patient that requires a cell graft in a manner that facilitates spreading of the cell suspension in a relatively even distribution over the graft region.” “Administering the suspension” does not mean spraying. It could mean dripping the suspension and allowing it to spread out. In any case, it refers to manual application of the

suspension, which is prone to inconsistent application as opposed to the flow controlled administration of the suspension set forth in the '430 patent as discussed in paragraphs 16, 28, and 60 above.

65. Dr. Shupp references Wood [0017]-[0019] and Example 1 of Wood ¶¶ [0100]-[0114] to support his assertion that “[t]he wound can be treated and healed without applying a preformed skin graft; that is, prior to spraying the droplets, no other skin graft was applied to the wound.” (Ex. 1007, ¶ 100).

66. However, a POSA would read Wood [0017]-[0019] and understand that it does not teach anything about “prior to spraying the droplets” or that “no other skin graft was applied to the wound.” It refers to “treating a patient in need of graft surgery” and “administering the suspension directly to a region on the patient that requires a cell graft in a manner that facilitates spreading of the cell suspension in a relatively even distribution over the graft region.” It does not state whether a graft is in the graft region or not when the administering takes place.

67. A POSA would understand that Example 1 of Wood ¶¶ [0100]-[0114] does not teach “*spraying the droplets [] so that the cells are distributed directly and evenly and the cells regenerate normal skin by in situ multiplication to heal the wounded area in the absence of applying a preformed skin graft.*”

68. As a preliminary matter, a POSA would observe that Example 1 of Wood teaches the use of a single enzyme for treating the tissue sample: trypsin.

(Ex. 1002, ¶ [0106].) As such, it does not teach the use of enzymes in the plural sense.

69. As another preliminary matter, Example 1 refers to a syringe and a nozzle for manual application (“spraying or dripping”) of the suspension, which is prone to inconsistent application as opposed to the flow controlled administration of the suspension set forth in the ’430 patent as discussed in paragraphs 16, 28, 60 and 64 above. (Ex. 1002, ¶¶ [0112], [0113].)

70. A POSA would understand that the use of sterile water for injection (10 ml) with the separation enzyme (lyophilised trypsin) to provide a 0.5% concentration of trypsin would result in a solution that promotes cell damage as such a solution would not be isotonic. A POSA would understand that a sterile buffered saline solution would be preferable to sterile water for this purpose. (See Wood, ¶ [0051]: “One such solution is preferably calcium and magnesium ion free phosphate buffered saline.”) A solution of trypsin in sterile water would be likely to reduce the viability of the cells, impairing the prospects for regeneration of normal skin via in situ multiplication to heal a wounded area. (Ex. 1007, ¶ 0106.)

71. Example 1 of Wood ¶¶ [0100]-[0114] is silent as to the aspects of healing the wounded area in the absence of applying a preformed skin graft. Instead, it states “to optimize the success of the skin graft” without describing the exact kind of skin graft. (Ex. 1002, ¶ [0101].) Wood describes the types of “skin

grafts” in the “Background Art” (Ex. 1002, ¶¶ [0004]-[0007]) and contrasts these skin grafting techniques to the use of a “cellular suspension.” (Ex. 1002, ¶ 0009.) Therefore, it is unclear in Example 1 whether or not the isolated cell suspension is being used as an adjunct to standard skin grafting techniques. Example 1 of Wood also references “the healing of the wound was followed up using standard protocols for skin-graft treatment” without explaining what the standard protocols include, nor providing any evidence that the treatment provided the patient with a positive outcome. (Ex. 1002, ¶ 0114.)

72. In paragraph 82 of the Shupp Declaration, Dr. Shupp states:

“The wound can be treated and healed without applying a preformed skin graft; that is, prior to spraying the droplets, no other skin graft was applied to the wound. *See* Wood, ¶¶ [0017]-[0019]. *See also* Example 1, ¶¶ [0100]-[0114] of Wood where no skin graft, other than spraying of the cell suspension, was applied to the wound.”

(Ex. 1007, ¶ 82.) As discussed above [¶66 and ¶71], these excerpts from Wood do not support the assertion that “no other skin graft was applied to the wound”.

Further, Dr. Shupp seems to interpret that “no other skin graft was applied to the wound” to mean “prior to spraying the droplets no other skin graft was applied to the wound.” However, as set forth in the Claim Constructions section of this declaration [¶38], his interpretation is incorrect. The ’430 patent provides a method to treat a wounded area of skin to heal the wounded area so that a

preformed skin graft is not necessary. This is consistent with how a POSA would interpret “to heal the wounded area in the absence of applying a preformed skin graft.” (See ¶¶ 32-38 of the Claim Constructions section, above.)

73. For at least these reasons Petition and Dr. Shupp fail to show that Wood teaches “*spraying the droplets [] so that the cells are distributed directly and evenly and the cells regenerate normal skin by in situ multiplication to heal the wounded area in the absence of applying a preformed skin graft*”.

### **C. Wood In View Of Lyles Does Not Render Claim 1 Obvious**

74. Dr. Shupp relies on “the identical reasons discussed above” to assert Wood for a

*“method to treat a wounded area of skin on a human subject, comprising providing a single cell-suspension of cells comprising progenitor skin cells in a serum-free physiological solution in a sterilizable container, wherein the cells are obtained from the subject's normal skin tissue that has been treated with enzymes so as to release the cells from the dermal-epithelial cell junction, wherein the skin cells have not been subjected to ex vivo or in vitro expansion”*

and

*“spraying the droplets onto the wounded area of skin without forming a closed cell sheet so that the single cells are distributed directly and evenly and the cells regenerate normal skin by in situ multiplication to*

*heal the wounded area in the absence of applying a preformed skin graft.”*

As set forth above, Dr. Shupp’s testing of Wood does not teach a single cell suspension, viability of cells, and similar morphology of the cells in the suspension both before and after spraying. The combination of Wood in view of Lyles also does not teach these things. Therefore, the combination of Wood in view of Lyles does not provide the elements of claim 1.

75. Dr. Shupp states that “[w]hile Wood may not have expressly disclosed ‘gas flow’ and ‘flow-controlled spray head,’ a POSA would have been motivated to employ the ‘air-jet sprayer’ of Lyles to deliver the suspension of Wood to the wound site with a reasonable expectation of success.” (Ex. 1007, ¶ 104.) However, a POSA would understand Lyles relates to approaches that create three-dimensional structures and full thickness grafts. (Ex. 1004, several places including ¶¶ [0040], [0041], [0045]-[0055], etc.) A POSA would understand that such sprays would likely be too thick to be evenly distributed and would likely form a closed cell sheet. Thus, applications of cells using the Lyles approach could create the problems of uneven cell distribution and blistering. (Ex. 1001, 4:45-46.) By analyzing the text of Shupp ¶¶ 105-108, it appears that three “motivations” are offered by Dr. Shupp, which are discussed in the following paragraphs.



76. The first “motivation” seems to be that Dr. Shupp asserts that Lyles and Wood relate to dispersing living cells onto an area of a subject, such as an open wound surface, and “a POSA would have been amply motivated with a reasonable expectation of success to employ the air-jet sprayer of Lyles, including the disclosed air flow mechanism, to spray the suspension of Wood.” (Ex. 1007, ¶¶ 105-108.) It seems that Dr. Shupp is asserting that since Lyles and Wood relate to spraying of cells, a POSA would have been motivated to combine them. That is an observation of applications of the references, but it does not explain a motivation to combine the references. Dr. Shupp’s assertion that a POSA would “employ the air-jet sprayer of Lyles, including the disclosed air flow mechanism, to spray the suspension of Wood” is conclusory and no rationale or factual basis is offered to explain why a POSA would combine them or why the POSA would combine them in the way specified by Dr. Shupp. For example, Dr. Shupp has not identified a reason why the syringe and nozzle of Wood does not work, and to the contrary he asserts that it does work to apply a “relatively even distribution over the graft region,” citing Wood ¶¶ [0017]-[0019] in his Declaration at paragraph 68. (See Ex. 1007, ¶ 68.) Therefore, Dr. Shupp’s first “motivation” is no motivation at all.

77. The second “motivation” seems to be that Dr. Shupp’s construction of a “flow-controlled spray head” includes any nozzle that aerosolizes a liquid, and Lyles creates an aerosol spray, and “a POSA would have been amply motivated

with a reasonable expectation of success to use the pressurized sprayer of Lyles because Lyles teaches that cell suspensions can be sprayed with such a device.” (Ex. 1007, ¶¶ 105-108.) As a preliminary matter, a POSA would disagree with the interpretations offered by Dr. Shupp (see Claim Constructions section, above). But even if they were considered for the sake of discussion, the assertion that one would combine the devices in the references as set forth by Dr. Shupp just because both aerosolize a liquid is not a motivation to combine them. Dr. Shupp’s reasoning here is conclusory and no rationale is offered to explain why a POSA would combine them or why the POSA would combine them in the way specified by Dr. Shupp. Indeed, Dr. Shupp has not identified any reason why the syringe and nozzle of Wood does not work, and asserts that it does in the previous arguments he provided in his Declaration. (See Ex. 1007, ¶ 68.) Therefore, Dr. Shupp’s second “motivation” is also not a motivation at all.

78. The third “motivation” seems to be that Dr. Shupp asserts that Wood discloses the use of a nozzle and a propellant fluid, and

“a POSA would have understood Lyles as disclosing devices suitable for creating droplets of the suspension at a flow-controlled spray head. [] Lyles discloses that ‘[i]nitial studies indicate that one may deliver live mammalian cells to a substratum with a hand held air-jet sprayer. The problems of drying droplets and nozzle clogging have been largely overcome by the use of a larger nozzle orifice and by the possible addition of dextran to the cell suspended media.’ See

Lyles, [0051]. Thus, a POSA would have had a reasonable expectation in combining Wood and Lyles.”

(Ex. 1007, ¶¶ 105-108.) However, Dr. Shupp does not assert that the syringe and nozzle of Wood suffer “problems of drying droplets and nozzle clogging.” Nor does his “motivation” explain why a POSA would substitute the Lyles apparatus for the syringe and nozzle of Wood. Therefore, Dr. Shupp’s Declaration does not provide a motivation for combination of Wood and Lyles by a POSA.

79. Accordingly, the Petition and Dr. Shupp fail to provide a rationale for why a POSA would combine Wood and Lyles as asserted, nor would such a combination overcome the deficiencies of Wood noted in my earlier analysis. Therefore, the Petition and Dr. Shupp fail to demonstrate that Wood in view of Lyles would provide the subject matter of claim 1. (Ex. 1007, ¶¶ 104-108.)

#### **D. Wood In View Of Navarro Does Not Render Claim 1 Obvious**

80. Dr. Shupp asserts:

“as Wood suggests the use of propellant fluids for contacting with the cell suspension and the use of nozzle to create droplets, a POSA would have been motivated to look to prior art devices for spraying cell suspensions which use propellant gases and would have had a reasonable expectation of success of contacting the cell suspension with a gas flow to produce aerosolized droplets at a flow-controlled spray head. Moreover, as shown below, all limitations of

claim 1 of the '430 patent are expressly taught by Wood in view of Navarro.”

(Ex. 1007, ¶ 109.) Dr. Shupp relies on “the identical reasons discussed above” to assert Wood “discloses or renders obvious each and every limitation of claim 1.”

(Ex. 1007, ¶¶ 109-111.) As set forth above, Dr. Shupp’s testing of Wood does not teach viability of cells, and similar morphology of the cells in the suspension both before and after spraying. The combination of Wood in view of Navarro also does not teach these things. Therefore, the combination of Wood in view of Navarro does not provide the elements of claim 1.

81. Dr. Shupp states that “[w]hile Wood may not have expressly disclosed ‘gas flow’ and ‘flow-controlled spray head,’ these elements are provided by Navarro, for nearly identical method to treat a wounded area of skin as the ’430 patent.” Dr. Shupp also asserts: “[a] POSA would have been motivated to employ the “spray apparatus” of Navarro to deliver the suspension of Wood to the wound site.” (Ex. 1007, ¶ 111.) Dr. Shupp’s alleged “motivation” is that “[a] POSA would have been motivated with a reasonable expectation of success to look to Navarro because both references are concerned with spraying cell suspensions onto wounds. Dr. Shupp concludes: “[a]ccordingly, a POSA would have been amply motivated with a reasonable expectation of success to use Navarro’s pressurized sprayer because Navarro teaches that a cell suspensions can be successfully sprayed with such a device and yield viable cells.” (Ex. 1007, ¶ 112.) However,

Dr. Shupp does not assert that the syringe and nozzle of Wood suffers any problem that Navarro solves. Nor has Dr. Shupp alleged that a POSA would find some advantage in Navarro motivating a POSA to combine Wood and Navarro. All Dr. Shupp appears to assert is Navarro teaches that cell suspensions can be sprayed with Navarro's hand-held pressurized sprayer and that such a device will yield viable cells, so a POSA would use it instead of the apparatus of Wood. (Ex. 1007, ¶¶ 109-113.) However, this does not provide a motivation to substitute the syringe and nozzle of Wood with Navarro's sprayer.

82. Accordingly, the Petition and Dr. Shupp fail to provide a rationale for why a POSA would combine Wood and Navarro as asserted, nor would such a combination overcome the deficiencies of Wood noted in the earlier analysis. Therefore, the Petition and Dr. Shupp fail to demonstrate that Wood in view of Navarro would provide the subject matter of claim 1. (Ex. 1007, ¶ 109-113.)

#### **E. Wood In View Of Dixon Does Not Render Claim 1 Obvious**

83. Dr. Shupp asserts:

“as Wood suggests the use of propellant fluids for contacting with the cell suspension and the use of nozzle to create droplets, a POSA would have been motivated to look to prior art devices for spraying cell suspensions which use propellant gases and would have had a reasonable expectation of success of contacting the cell

suspension with a gas flow to produce aerosolized droplets at a flow-controlled spray head. Moreover, as shown below, all limitations of claim 1 of the '430 patent are expressly taught by Wood in view of Dixon.”

(Ex. 1007, ¶ 114.) Dr. Shupp relies on “the identical reasons discussed above” to assert Wood “discloses or renders obvious each and every limitation of claim 1.”

(Ex. 1007, ¶¶ 114-116.) As set forth above, Dr. Shupp’s testing of Wood does not teach a single cell suspension, viability of cells, and similar morphology of the cells in the suspension both before and after spraying. The combination of Wood in view of Dixon also does not teach these things. Therefore, the combination of Wood in view of Dixon does not provide the elements of claim 1.

84. Dr. Shupp states that “[w]hile Wood may not have expressly disclosed ‘gas flow’ and ‘flow-controlled spray head,’ these elements are provided by Dixon, for nearly identical method to treat a wounded area of skin as the ’430 patent.” Dr. Shupp also asserts: “[a] POSA would have been motivated to employ the “cell spray apparatus” of Dixon to deliver the suspension of Wood to the wound site.” (Ex. 1007, ¶ 116.) Dr. Shupp’s alleged “motivation” is that “[a] POSA would have been amply motivated with a reasonable expectation of success to employ the sprayer of Dixon, to apply the suspension of Wood.” (Ex. 1007, ¶ 118.) Dr. Shupp concludes: “[a]ccordingly, a POSA would have been amply motivated with a reasonable expectation of success to use the pressurized sprayer of Dixon

because Dixon teaches that cell suspensions can be sprayed with such a device comprising a flow-controlled spray head.” (Ex. 1007, ¶¶ 114-118.) However, Dr. Shupp is employing his definition of a “flow-controlled spray head” which is incorrect, as set forth in the Claim Constructions section. For example, Dr. Shupp does not assert that the syringe and nozzle of Wood suffers any problem that Dixon solves, nor has Dr. Shupp alleged that a POSA would find some motivation to combine Wood in view of Dixon. All Dr. Shupp appears to assert is that Dixon teaches that cell suspensions can be sprayed with Dixon’s pressurized sprayer, so a POSA would use it instead of the apparatus of Wood. (Ex. 1007, ¶¶ 114-119.) However, this does not provide a motivation to substitute the syringe and nozzle of Wood with Dixon’s sprayer.

85. Accordingly, the Petition and Dr. Shupp fail to provide a rationale for why a POSA would combine Wood and Dixon as asserted, nor would such a combination overcome the deficiencies of Wood noted in the earlier analysis. Therefore, the Petition and Dr. Shupp fail to demonstrate that Wood in view of Dixon would provide the subject matter of claim 1. (Ex. 1007, ¶¶ 114-119.)

#### **F. Wood In View Of Marshall Does Not Render Claim 1 Obvious**

86. Dr. Shupp asserts:

“as Wood suggests the use of propellant fluids for contacting with the cell suspension and the use of nozzle to create droplets, a POSA would have been motivated to look to prior art devices for spraying cell suspensions which use propellant gases and would have had a reasonable expectation of success of contacting the cell suspension with a gas flow to produce aerosolized droplets at a flow-controlled spray head. Moreover, as shown below, all limitations of claim 1 of the ‘430 patent are expressly taught by Wood in view of Marshall.” (Ex. 1007, ¶ 120.) Dr. Shupp relies on “the identical reasons discussed above” to assert Wood “discloses or renders obvious each and every limitation of claim 1.” (Ex. 1007, ¶¶ 120-122.) As set forth above, Dr. Shupp’s testing of Wood does not teach a single cell suspension, viability of cells, and similar morphology of the cells in the suspension both before and after spraying. The combination of Wood in view of Marshall does not teach these things. Therefore, the combination of Wood in view of Marshall does not provide the elements of claim 1.

87. Dr. Shupp states that “[w]hile Wood may not have expressly disclosed ‘gas flow’ and ‘flow-controlled spray head,’ these elements are provided by Marshall, for nearly identical method to treat a wounded area of skin as the ‘430 patent.” Dr. Shupp also asserts: “[a] POSA would have been motivated to employ the “spraying apparatus” of Marshall to deliver the suspension of Wood to the wound site.” (Ex. 1007, ¶¶ 120-122.) Dr. Shupp’s alleged “motivation” is that “[a] POSA would have been amply motivated with a reasonable expectation of



success to employ the sprayer of Marshall, to apply the suspension of Wood.” (Ex. 1007, ¶¶ 120-124.) Dr. Shupp concludes: “[a]ccordingly, a POSA would have been amply motivated with a reasonable expectation of success to use the pressurized sprayer of Marshall because Marshall teaches that cell suspensions can be sprayed with such a device.” (Ex. 1007, ¶ 124.) However, Dr. Shupp does not assert that the syringe and nozzle of Wood suffers any problem that Marshall solves. All Dr. Shupp appears to assert is that Marshall teaches cell suspensions can be sprayed with Marshall’s pressurized sprayer, so a POSA would use it instead of the apparatus of Wood. (Ex. 1007, ¶¶ 120-125.) However, this does not provide a motivation to substitute the syringe and nozzle of Wood with Marshall’s sprayer.

88. Accordingly, the Petition and Dr. Shupp fail to provide a rationale for why a POSA would combine Wood and Marshall as asserted, nor would such a combination overcome the deficiencies of Wood noted in the earlier analysis. Therefore, the Petition and Dr. Shupp fail to demonstrate that Wood in view of Marshall would provide the subject matter of claim. (Ex. 1007, ¶ 120-125.)

## **G. Wood and the Wood plus Lyles, Navarro, Dixon, and Marshall**

### **Combinations Do Not Render Claims 2-11 Obvious**

89. The Petitioner and Dr. Shupp fail to demonstrate that claim 1 is obvious over Wood, Wood in view of Lyles, Wood in view of Navarro, Wood in view of Dixon, and Wood in view of Marshall. (Ex. 1007, ¶ 126.) I have been advised that if claim 1 is patentable over the prior art grounds based on Wood, Wood in view of Lyles, Wood in view of Navarro, Wood in view of Dixon, and Wood in view of Marshall, then claims 2-11 are not rendered unpatentable by these same reference combinations. Accordingly, claims 2-11 are not obvious over these reference combinations, and I will comment only on the statements made about the dependent claims where it seems that clarification may be helpful.

90. Claims 2, 3, 4, 5, and 6 relate to the nature of cells found in the suspension. Dr. Shupp's attempt to perform the method of Wood should have afforded him the opportunity to scientifically assess the nature of the cells in suspension, especially as related to their viability. However, the paragraphs following Ex. 1007, ¶ 126 do not discuss experimental findings by Dr. Shupp. A POSA would suspect the suspension provided by Wood may not have exhibited the nature of cells recited in claims 2, 3, 4, 5, and 6 for at least the reasons set forth herein (and especially in light of how the process of Example 1 of Wood potentially compromises the viability of the cells). A POSA would understand that

the viability could have been scientifically measured to assess it insofar as it relates to the morphology as recited in claim 4, but no viability test results were provided. As stated above, a POSA would understand that the microscopic slide comparisons do not confirm morphology, and so a POSA would disagree with the conclusions Dr. Shupp has reached with regard to them, which were referenced again in Ex. 1007, ¶ 134. (See paragraph 50, above.) Therefore, Dr. Shupp's findings relating to the suspension derived from the method of Wood are incomplete and misleading.

91. With regard to Ex. 1007, ¶¶ 143-146, a POSA would disagree with the way that Dr. Shupp has determined filter cutoff. (See paragraph 47, above.)

92. Wood relates to a single enzyme approach, and the analysis in paragraphs 55-63 above applies to Ex. 1007, ¶¶ 147-150.

93. In Ex. 1007, ¶¶ 151-156, Dr. Shupp concludes that "Wood discloses that the suspension can be delivered by continuous force application to the container such as a syringe." (Ex. 1007, ¶ 154.) A POSA would find it difficult to apply a continuous, even force to a syringe by hand. A POSA would understand the amount of resistance that a plunger of a syringe applies can vary substantially over its course of travel, resulting in uneven flow and control of the material being delivered. The leverage of force applied also varies with the angle of compression that the fingers have with respect to the syringe and its plunger, also complicating

any attempt to apply a continuous force to a syringe. Thus, A POSA would experience varying forces to operate a syringe as set forth in Ex. 1007, ¶ 154. A POSA would understand the same can be said of the plastic actuator or nozzle of Navarro discussed in Ex. 1007, ¶ 155. Therefore, a POSA would find it difficult to manually apply a continuous force application to a syringe container of Navarro and with the proposed combination of Wood and Navarro.

94. For at least all of the foregoing reasons, claims 1-11 of the '430 patent are not obvious to a POSA over each of Wood, Wood in view of Lyles, Wood in view of Navarro, Wood in view of Dixon, and Wood in view of Marshall.

I, Dr. Gary D. Shipley, do hereby declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true and, further, that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: September 19, 2017

/Gary D. Shipley/  
Dr. Gary D. Shipley