

Paper No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Avita Medical Limited
Petitioner

v.

RenovaCare Sciences Corp.
Patent Owner

Patent No. 9,610,430 (Claims 1-11)

Filed: December 20, 2013

Inventor: Reinhard Bornemann

Title: CELL SPRAYING DEVICE, METHOD AND SPRAYED CELL
SUSPENSION

Inter Partes Review No. IPR2017-01243

PETITION FOR INTER PARTES REVIEW

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Attachment A. Proof of Service of the Petition

Attachment B. List of Evidence and Exhibits Relied Upon in Petition

TABLE OF AUTHORITIES

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Cases	
<i>KSR Int’l Co. v. Teleflex</i> , 550 U.S. 398 (2007).....	41, 48, 57, 64
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I. Compliance with Requirements of *Inter Partes* Review Petition

A. Certification that the Patent May Be Contested via *Inter Partes* Review by the Petitioner (37 CFR §§ 42.101 and 42.104)

Petitioner certifies that U.S. Patent No. 9,610,430 (“the ‘430 patent”) [Ex. 1001]) is available for review and that Petitioner is not barred or estopped from requesting *inter partes* review of any of the claims of the ‘430 patent. Neither Petitioner, nor Petitioner’s real party in interest, nor any privy of Petitioner: (a) has filed a civil action challenging the validity of any of the claims of the ‘430 patent; (b) has been served a complaint alleging infringement of the ‘430 patent more than a year prior to the present date; or (c) is estopped from challenging any of the claims of the ‘430 patent.

B. Fee for *Inter Partes* Review (37 CFR § 42.15(a))

The Director is authorized to charge the fee specified by 37 CFR §42.15(a) to Deposit Account No. 50-1561, which fee is believed to be \$23,000. Any necessary additional fees may be charged to Deposit Account No. 50-1561.

C. Mandatory Notices (37 CFR § 42.8(b))

1. Real Party in Interest (37 CFR § 42.8(b)(1))

The real party of interest of this petition is *Avita Medical Limited*, an Australian company having a subsidiary, Avita Medical Americas LLC at the address of 28159 Avenue Stanford, Suite 220, Valencia, CA 91355 (“Petitioner”). No other entity is a real party of interest or a privy for purposes of this petition.

2. Other Proceedings (37 CFR § 42.8(b)(2))

To Petitioner's knowledge, the '430 patent is not presently the subject of other proceedings.

3. Lead and Backup Lead Counsel (37 CFR § 42.8(b)(3))

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4. Service Information (37 CFR § 42.8(b)(4))

Service on Petitioner may be made by mail or hand delivery to: Greenberg Traurig, LLP, 200 Park Avenue, New York, NY 10166. Petitioner also consents to service by email to: njdocket@gtlaw.com.

D. Proof of Service (37 CFR §§ 42.6(e) and 42.105(a))

Proof of service of this petition is provided in **Attachment A**.

II. Identification of Claims Being Challenged (37 CFR § 42.104(b))

Claims 1-11 of the '430 patent are unpatentable for the following reasons:

- Claims 1-11 are obvious under 35 U.S.C. §103 (pre-AIA) over U.S.

Publication No. 2002/0106353 to Wood et al. (hereafter, "Wood") [**Ex.**

1002].

- Claims 1-11 are obvious under 35 U.S.C. §103 (pre-AIA) over Wood in view of Navarro et al., “Sprayed Keratinocyte Suspensions Accelerate Epidermal Coverage in a Porcine Microwound Model,” *Journal of Burn Care & Rehabilitation*, November/December 2000, 21(6):513-518 (hereafter, “Navarro”) [**Ex. 1003**].
- Claims 1-11 are obvious under 35 U.S.C. §103 (pre-AIA) over Wood in view of U.S. Publication No. 2004/0219133 to Lyles (hereafter, “Lyles”) [**Ex. 1004**].
- Claims 1-11 are obvious under 35 U.S.C. §103 (pre-AIA) over Wood in view of U.S. Patent No. 7,833,522 to Dixon (hereafter, “Dixon”) [**Ex. 1005**].
- Claims 1-11 are obvious under 35 U.S.C. §103 (pre-AIA) over Wood in view of U.S. Patent No. 6,479,052 to Marshall (hereafter, “Marshall”) [**Ex. 1006**].

Wood, Navarro, Lyles, and Marshall each constitutes prior art to the ‘430 patent under 35 U.S.C. §102(b) (pre-AIA) because each was published more than one year prior to the earliest claimed priority date of the ‘430 patent. Dixon is prior art to the ‘430 patent under 35 U.S.C. §102(e) (pre-AIA).

A list of evidence relied upon in support of this petition is set forth in

Attachment B.

A Declaration of Jeffrey W. Shupp, M.D. regarding the invalidity of the ‘430 patent (“Shupp Decl.”), along with his CV and materials relied on and considered are included herewith as **Exs. [1007] and [1008]**. Dr. Shupp is the Director of the Burn Center at MedStar Washington Hospital Center and an attending surgeon in the Burns/Trauma section of surgery. Dr. Shupp is also the Director of Burn Research at MedStar Health Research Institute and the lead investigator at the Firefighters’ Burn and Surgical Research Laboratory. He is additionally an assistant professor of Biomedical Engineering at The Catholic University of America and an instructor of surgery at the Uniformed Services University of the Health Sciences. Dr. Shupp specializes in skin grafting and treating burns, trauma to the skin, including electrical and chemical injuries, complex wounds, and other skin disorders that result in skin loss.

Petitioner’s proposed claim constructions, evidence relied upon, and precise reasons why the claims are unpatentable, are set forth below in **Section III**.

III. Relevant Information Concerning the Contested Patent

A. Person of Ordinary Skill in the Art

In this case, a person of ordinary skill in the art (“POSA”) would be a medical doctor specializing in skin injury, skin grafting and wound care.

B. Prosecution History of the ‘430 Patent

While the primary prior art reference at issue in this Petition, Wood, was

used by the Examiner during prosecution as a secondary reference, it is clear that the Examiner did not apprehend the full disclosure of Wood. Specifically, the Examiner's principle rejection of the claims was based on anticipation and obviousness over Lyles. Wood was used only as a secondary reference to show the use of specific cell types in wound healing, but was never cited alone, or as a primary reference. A copy of the file history of the '430 patent is included herewith as [Ex. 1009].

The prosecution history makes abundantly clear that the '430 patent was allowed based on the Examiner's incorrect determination that a single claim limitation—"wherein the skin cells have not been subjected to ex vivo or in vitro expansion"—was allegedly lacking in the prior art's teachings. *See* November 25, 2016 Notice of Allowance, p. 2 ("The "closest prior art of record Lyles ['133], Wood ['353] ... fail to teach, suggest or render obvious the method, *wherein the skin cells have not been subjected to ex vivo or in vitro expansion*" (emphasis added)). However, the Examiner overlooked the fact that this claim limitation was expressly disclosed in Wood: "...the cell population within the suspension is ***not expanded*** prior to application to the graft site. Rather cellular multiplication is encouraged on the patient ***rather than in an in vitro system***." *See* Wood, ¶ [0061] (emphasis added). Had the Examiner recognized this teaching in Wood, the application for the '430 patent would not have been allowed.

C. Construction of Terms Used in the Claims

The earliest claimed priority date of the ‘430 patent is September 11, 2006, and therefore it has an apparent expiration date of November 12, 2026. As such, the “broadest reasonable construction” standard of 37 C.F.R. § 42.100(b) is applicable.

1. General Observations

Petitioner sets forth below several preliminary claim constructions pertinent to the validity analysis under the “broadest reasonable construction” standard. However, Petitioner reserves the right to change or amend these constructions in any litigation concerning the ‘430 patent, as discovery and expert testimony may shed additional light on how these terms would have been understood by a POSA. Furthermore, by offering these constructions, Petitioner does not concede that the specific terms construed, or other terms in the claims, are definite. To the contrary, Petitioner believes that many of the terms are fatally indefinite and reserves all rights to fully argue indefiniteness in any litigation.

2. Constructions

a. “single cell-suspension”

The ‘430 patent does not offer a specialized definition of the term “single cell-suspension.” While Petitioner reserves the right to argue in any litigation that this term is indefinite under 35 U.S.C. 112 (pre-AIA), 2nd paragraph, the following

construction is submitted for purposes of this Petition only.

As an initial matter, “single cell-suspension” is regarded as the same as “single-cell suspension,” as the latter term was also used in claim 1. That is, the location of the hyphen in the phrase “single cell-suspension” is believed to be an error.

The ‘430 patent does not offer a specialized definition of the term “single-cell suspension.” Under the plain and ordinary meaning of this term to a POSA, it could refer to: (1) a suspension of a single *type* of cells, and/or (2) a suspension of individual cells (*i.e.*, cells that are not adhered, or otherwise associated with each other). *See* Shupp Decl. ¶ 40. However, the first of these possible meanings is precluded by the claims themselves. Specifically, dependent claim 2 specifies that the “suspension comprises uncultured cells types in a ratio comparable to that found in normal skin.” Thus, the “single-cell suspension” of claim 1 must embrace multiple types of cells. Further, dependent claim 3 recites that the cells in the suspension comprise “basal keratinocytes, Langerhans cells, fibroblasts, and melanocytes.” Inasmuch as claims 2 and 3 require the suspension to comprise multiple different types of cells, the term “single-cell suspension” cannot be construed as limited to a single *type* of cells, under the doctrine of claim differentiation. Thus, in the context of the ‘430 patent, the plain and ordinary

meaning—a suspension comprising individual cells that are not adhered to, or otherwise associated with, each other—should apply for purposes of this proceeding. *See* Shupp Decl. ¶ 40. This construction is consistent with the specification of the ‘430 patent. For example, the ‘430 patent discloses: “Using individually-sprayed cells ..., rather than confluent grown keratinocyte sheets as in the prior art, results in the need for fewer cells and application to a larger treatment surface.” *See* col. 4, lns. 41-46. A POSA would understand this disclosure to equate “single cells” with *individual* cells, as contrasted with cells that are associated with others (*e.g.*, a “sheet” of cells). *See* Shupp Decl. ¶ 43. 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. *See* Shupp Decl. ¶ 43.

b. “progenitor skin cells” / “skin progenitor cell”

The ‘430 patent does not offer a specialized definition of the terms “progenitor skin cells” or “skin progenitor cells” and thus, these terms carry their plain and ordinary meaning to a POSA, referring to progenitor cells of the skin. *See* Shupp Decl. ¶ 44. A “progenitor cell” is understood by a POSA to mean a “biological cell capable of self-renewal, *i.e.*, reproduction or proliferation, and is often used interchangeably with “stem cell.” *See* Shupp Decl. ¶ 44. Progenitor cells are inherently present in skin tissue, such as those located within the dermal-

epithelial junction. *See* Shupp Decl. ¶ 44. Accordingly, “progenitor skin cells” or “skin progenitor cells” include skin cells capable of reproduction, including without limitation, such skin cells located within the dermal-epithelial junction. *See* Shupp Decl. ¶ 44.

Petitioner notes that Claim 1 uses the term “progenitor skin cells,” whereas Claim 5 uses the term “skin progenitor cells.” The ‘430 patent does not explain any difference in the meaning of these terms and a POSA would not be aware of any difference. *See* Shupp Decl. ¶ 45. Accordingly, for the purposes of the present Petition only, the terms are construed as synonymous. Consequently, Petitioner reserves the right to argue that Claim 5 is invalid under 35 U.S.C. §112, ¶4 as failing to limit the claim from which it depends.

c. “*ex vivo* or *in vitro* expansion”

The ‘430 patent does not offer a specialized definition of the term “*ex vivo* or *in vitro* expansion” and thus, it carries its plain and ordinary meaning to a POSA. “*Ex vivo*” means the use or positioning of a tissue or cell after removal from an organism while the tissue or cells remain viable. [Ex. 1011]. “*In vitro*” means use of the cells outside the normal biological context, *i.e.*, in an artificial environment. [Ex. 1012]. The term “*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. *See* Shupp Decl. ¶ 47. These

constructions are further supported by the prosecution history of the ‘430 patent. See November 1, 2016 “Amendment and Response under 37 CFR § 1.116,” at p. 7, [Ex. 1009 at p.] (“*Ex vivo* is recognized to be ‘out of the body’ and *in vitro* is recognized to be ‘in an artificial environment.’”).

d. “a gas flow”

The ‘430 patent does not offer a specialized definition of the phrase “a gas flow” and thus, under the broadest reasonable construction, it carries its plain and ordinary meaning to a POSA, referring in the context of the ‘430 patent to the flow of a propellant gas that forces the suspension through a flow-controlled spray head. See Shupp Decl. ¶ 49. This is supported by the specification of the ‘430 Patent, which discloses that “the apparatus can be operated by producing a gas flow, for example air from a compressor, to engage the spray head.” See col. 4, lns. 34-36.

e. “flow-controlled spray head”

The ‘430 patent does not offer a specialized definition of the term “flow-controlled spray head” and thus, it carries its plain and ordinary meaning to a POSA, referring to a spray device which controls or regulates the flow of a fluid therethrough. See Shupp Decl. ¶ 50. The term would include, for example, a “nozzle,” which by definition, is “a device designed to control the direction or characteristics of a fluid flow (especially to increase velocity) as it exits (or enters) an enclosed chamber or pipe.” [Ex. 1014]. Accordingly, under the broadest

reasonable construction, a “flow-controlled spray head,” includes a spray nozzle. This construction is consistent with the specification of the ‘430 patent which discloses that 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.” *See* col. 7, lns. 21-24 (emphasis added).

f. “closed cell sheet”

The ‘430 patent does not offer a specialized definition of the term “closed cell sheet.” However, without conceding that the term is definite, and under the broadest reasonable construction standard, the term would be understood to refer to a collection of adherent cells in the form of a sheet structure. *See* Shupp Decl. ¶ 53. This construction is consistent with the specification of the ‘430 patent, which discloses: “Using individually-sprayed cells ..., rather than confluent grown keratinocyte sheets as in the prior art, results in the need for fewer cells and application to a larger treatment surface.” col. 4, ln. 41-46. Accordingly, a “closed cell sheet” would be understood to be a continuous sheet of cells.

g. “preformed skin graft”

The ‘430 patent does not offer a specialized definition of the term “preformed skin graft” and thus, it carries its plain and ordinary meaning to a POSA, referring to any skin graft, such as a split-thickness graft, full-thickness

graft, mesh graft, micro-grafting, and cultured epithelial autografts, that is formed prior to application to the wound site. *See* Shupp Decl. ¶ 54.

h. “comparable”

The ‘430 patent does not offer a specialized definition of the term “comparable” and does not provide any guidance on how to determine whether cell types in the suspension are in a ratio “comparable” to that of a normal skin. *See* Shupp Decl. ¶ 55. Petitioner therefore reserves the right to argue in any litigation that this term is indefinite under 35 U.S.C. 112 (pre-AIA), 2nd paragraph. Petitioner submits the following construction for purposes of this Petition only.

For the purposes of this Petition, a “comparable” ratio of cell types is regarded as a ratio of cell types that substantially mirrors the ratio of cell types in the skin, as there has been no selective culturing of a specific cell type. This construction is supported by the ‘430 patent which discloses, “[w]hereas conventional methods lose cellular constituents, such as skin progenitor cells, because of selective culture for keratinocytes, the cellular suspension contemplated in the current invention has a cell composition comparable to the in situ cell population.” ¶ [0049]; *See* Shupp Decl. ¶ 56.

i. “morphology”

The ‘430 patent does not offer a specialized definition of the term “morphology” and thus, it carries its plain and ordinary meaning to a POSA,

referring, in the context of cells, to the size, shape and structure of cells. *See* Shupp Decl. ¶ 57. This construction is consistent with the specification of the ‘430 patent which discloses: “Cell morphology was monitored by light microscopy (ZEISS, AXIOVERT 25). Sprayed and non-sprayed cells showed similar morphologic appearance in light- and phase-contrast microscopy; they also showed comparable follow up culture behavior.” *See* col. 8, lns. 49-53. A POSA would understand that these microscopy techniques analyze the size and shape the cells. *See* Shupp Decl. ¶ 58.

j. “similar”

The ‘430 patent does not offer a specialized definition of the term “similar” and does not provide any guidance on how to determine whether cell morphology is “similar.” Petitioner therefore reserves the right to argue in any litigation that this term is indefinite under 35 U.S.C. 112 (pre-AIA), 2nd paragraph. Nevertheless, Petitioner submits the following construction for purposes of this Petition only.

A “similar” morphology is understood, under the broadest reasonable construction, to be a less exacting standard than “identical,” and permit a limited degree of alteration in the morphology of the cells that would be immaterial to the functionality of the suspension. *See* Shupp Decl. ¶ 60. A POSA would further understand from the ‘430 patent that cells of “similar morphologic appearance” were of comparable viability to cells in the suspension, as measured by culturing.

See col. 8, lns. 49-53. *See also* Shupp Decl. ¶ 60.

Accordingly, solely for the purposes of this Petition, and under the broadest reasonable construction standard, a “morphology that is similar to the cells in the droplets,” means that the size, shape and structure of the cells in the suspension and the droplets are essentially the same as measured by light- and phase-contrast microscopy, and that any differences do not impair the viability of the cells in the suspension.

k. “large cellular congregates”

The ‘430 patent does not offer a specialized definition of the term “large cellular congregates” and fails to provide any guidance on how to determine what size is “large.” Petitioner therefore reserves the right to argue in any litigation that this term is indefinite under 35 U.S.C. 112 (pre-AIA), 2nd paragraph.

The only disclosure in the ‘430 patent pertinent to this term merely states that “[a]ny filter capable of separating excessively large cellular congregates from the suspension may be used. The filter may exhibits a cut off of about 5 cells to about 100 cells, preferably about 20 to about 60 cells and most preferably about 40 cells.” *See* ‘430 patent, col. 7, lns. 51-55. While the cited disclosure relates to “excessively large” congregates, for the purposes of this Petition only, under the broadest reasonable construction, “large” cellular congregates are regarded as

congregates of five or more cells, consistent with the filter cutoffs disclosed in the ‘430 patent. *See* Shupp Decl. ¶ 63.

I. “continuous force application”

The ‘430 patent does not offer a specialized definition of the term “continuous force application,” other than to indicate that the force is applied “over a range of about 0.5 to about 10±1.0 minutes.” col. 7, lns. 34-36.. Thus, without conceding that the phrase is definite, and only under the broadest reasonable construction, the phrase may be understood to mean the application of force, manually or otherwise, continuously for about 30 seconds to about 10 minutes. *See* Shupp Decl. ¶ 65.

D. Effective Filing Date

The ‘430 patent purports to claim priority, as a continuation, to earlier filed application U.S. Patent Application No. 11/518,012, filed on September 11, 2006. Petitioner does not concede, and expressly denies, that the claims are entitled to priority. For present purposes, however, Petitioner treats September 11, 2006 as the relevant date for determining prior art.

E. Claims 1-11 Are Rendered Obvious by Wood

Every element of claims 1-11 of the ‘430 patent is taught, suggested or rendered obvious by prior art reference Wood. Wood is prior art to the ‘430 patent

under 35 U.S.C. §102(b) (pre-AIA) because it published on August 8, 2002—more than one year prior to the September 11, 2006 earliest claimed priority date of the ‘430 patent. Claims 1-11 of the ‘430 patent are invalid as obvious under 35 U.S.C. §103 over Wood.

1. The Teachings of Wood

Wood is directed to a “technique for grafting of cells, and in particular to a device for preparing a suspension of cells from a tissue sample obtained from a donor site and applying that suspension of cells to a recipient cite.” Wood, ¶ [0002]. Wood “provides a means for the treatment various skin disorders or disease” including “burn wounds.” Wood, ¶ [0044]. Such treatment method can include “(a) preparing [a] cell suspension . . . ; [and] (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.” Wood, ¶¶ [0017]-[0019].

Wood’s method of preparing a cell suspension can comprise the following steps:

- (a) 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;

- (b) removing the sample from the enzyme solution used in step (a) and harvesting in the presence of a nutrient solution cells from the tissue sample, which cells are suitable for grafting on to a patient wherein the nutrient solution is (i) free of xenogenic serum, (ii) capable of maintaining the viability of the cells until applied to a patient and (iii) is suitable for direct application to a region on a patient undergoing tissue grafting;
- (c) filtering the cellular suspension produced according to step (b) to remove large cellular conglomerates.

See Wood, ¶¶ [0020]-[0023].

The tissue sample is “preferably of an autologous nature” and “is harvested from a patient by means known in the art of tissue grafting.” Wood, ¶ [0048]. By “autologous” graft, it is meant that “tissue is taken from one area of the body and applied to another area.” Wood, ¶ [0003]. That is, a tissue sample taken from the patient’s normal skin tissue can be processed to provide a cell suspension for application back to the same patient, at the burn site. *See* Shupp Decl. ¶ 70.

Enzymes suitable for dissociating tissue stratum include “trypsin, dispase, [and] collagenase.” *See* Wood, ¶¶ [0050]-[0051]. Thereafter, “[c]ells capable of reproduction are then removed from the separated stratum by any means known in the art. ... Cells capable of reproduction within the dermal-epithelial junction include but are not limited to keratinocyte basal cells, Langerhans cells, fibroblasts and melanocytes.” Wood, ¶ [0057]. A POSA would recognize that cells capable of

reproduction within the dermal-epithelial junction inherently include progenitor skin cells. *See* Shupp Decl. ¶ 71.

“Following release of the cells from the tissue sample they are suspended in the nutrient solution.” Wood, ¶ [0057]. “Preferably, the nutrient solution is free of all serum but contains various salts that resemble the substances found in body fluids; this type of solution is often called physiological saline.” Wood, ¶ [0055]. Wood explains that the use of a 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: “Such serum is...generally required for the *in vitro* expansion of the cells.... The nutrient solution used in the present invention does not require such serum because the cell population within the suspension is not expanded prior to application to the graft site. Rather cellular multiplication is encouraged on the patient rather than in an *in vitro* system.” *See* Wood, ¶ [0061]. Thus, a POSA understands that the cells in Wood’s suspension are not subjected to *ex vivo* or *in vitro* expansion. *See* Shupp Decl. ¶ 73.

The cell suspension is then filtered using “[a]ny filter capable of separating excessively large cellular congregates from the suspension.” *See* Wood, ¶ [0058]. For example, “the filter size is between 50 μm and 200 μm .” *Id.* Wood’s 50 μm filter size would be understood by a POSA to have a cut-off of about 2 cell congregates, which would imply that the suspension comprises mainly single cells

where such a filter is used. *See* Shupp Decl. ¶ 74. The 200 µm filter size of Wood would be understood by a POSA to correspond to a cut-off of, at the cross section, about 65 cell congregates. *See* Shupp Decl. ¶ 74.

That Wood discloses a “single-cell suspension” is further confirmed by Dr. Shupp's replication of the steps of Example 1 (¶¶ [0100]-[0112]) of Wood, using the ReCell® Rapid Technique cell harvesting apparatus, Dr. Shupp demonstrates by microscopy that the resulting suspension contained single cells. *See* Shupp Decl. ¶ 75.

The filtered, single-cell suspension may then “be aspirated into” a container such as “a syringe and applied to the recipient site.” Once the single-cell suspension is “aspirated into a syringe” a “nozzle” can be “attached to the syringe for spraying or dripping on to the wound area.” Wood, ¶ [0112]. According to Wood, the nozzle can be “any type of nozzle that transforms liquid into small airborne droplets.” *See* Wood, ¶ [0064]. *See* Shupp Decl. ¶ 77; *See* §III(C)(1)(e), *supra*.

Wood teaches that when using a nozzle, two constraints may apply: “First, it must not subject the cells in solution to shearing forces or pressures that would damage or kill substantial numbers of cells. Second, it should not require that the cellular suspension be mixed with a propellant fluid that is toxic or detrimental to cells or wound beds.” *See* Wood, ¶ [0064]. Based on this disclosure, a POSA

would understand that the cells in the suspension will have a morphology that is similar to the cells in the droplets because the cells remain viable. *See* Shupp Decl. ¶ 78. Indeed, Dr. Shupp’s replication of the Examples of Wood demonstrates that before and after spraying a suspension made using the ReCell® Rapid Technique of Wood through a nozzle, the morphology of the cells in the suspension is similar to the morphology of the cells in the droplets. *See* Shupp Decl. ¶ 80.

According to Wood, “cells suitable for grafting back to a patient are collected and dispersed in a solution that is suitable for immediate dispersion over the recipient graft site.” *See* Wood, ¶ [0038]. Because the cells are mainly in the form of individual cells dispersed in a solution, they inherently fail to form a closed cell sheet, *i.e.*, a collection of adherent cells in the form of a sheet structure. *See* Shupp Decl. ¶ 80. Indeed, Dr. Shupp’s replication of Wood’s Example 1 demonstrates that by spraying through the nozzle of Wood’s apparatus, no closed cell sheet is formed on the wound. *See* Shupp Decl. ¶ 81. Rather, 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.” Wood, ¶ [0019].

Wood’s cell suspension is “suitable for use in resurfacing and regeneration of damaged tissue” and “is highly suitable for tissue regeneration and grafting techniques.” Wood, ¶¶ [0047], [0060]. In using the cell suspension of Wood, “a wound...can be treated quickly by in situ multiplication of a limited number of

cells.” Wood, ¶ [0060]. The wound can be treated and healed without applying a preformed skin graft; that is, prior to spraying the droplets, no other skin graft is applied to the wound. *See* Wood, ¶¶ [0017]-[0019]. *See also* Example 1, ¶¶ [0100]-[0114], wherein no skin graft, other than spraying of the cell suspension, was applied to the wound.

One advantage of Wood is that it can “produce a suspension of cells in a ratio to each other comparable with those seen in situ....One possible explanation for this is that in the prior art, culture of the cellular preparation utilises selective culture for keratinocytes, therefore loss of cellular constituents such as fibroblasts and melanocytes occurs whereas the cellular suspension produced from the first aspect of the invention has a cell composition comparable to the in situ cell population.” Wood, ¶¶ [0045], [0062]. A POSA would understand this to mean that, 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. *See* Shupp Decl. ¶ 83.

2. Wood Renders Obvious Claim 1

Wood teaches, suggests or renders obvious every limitation of claim 1 as further shown below.

Claim 1 of the ‘430 patent is reproduced below:

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.

a. “A method to treat a wounded area of skin on a human subject comprising...”

Wood discloses “a method for treating a patient using the unique cell suspension,” as well as “a means for the treatment of various skin disorders or diseases,” including “burn wounds.” See Wood, ¶¶ [0010], [0044]. Accordingly, Wood discloses the limitation of “a method to treat a wounded area of skin on a human subject.” See Shupp Decl. ¶ 85.

b. “...providing a single cell-suspension...”

Wood discloses filtering the cell suspension using “[a]ny filter capable of separating excessively large cellular congregates from the suspension.” *See* Wood, ¶ [0058]. For example, “the filter size is between 50 μm and 200 μm .” *Id.* As explained by Dr. Shupp, the average diameter of human skin cells is about 30 μm and generally ranges from 25-40 μm . *See* Shupp Decl. ¶ 86. *See also* [Ex. 1013]. A POSA would understand that a 50 μm filter permits the passing of individual human skin cells but removes most congregates of 2 or more cells, leaving mainly individual cells that are not adhered to, or otherwise associated with each other. Accordingly, the filters sizes disclosed in Wood would inherently result in a single-cell suspension of cells. *See* Shupp Decl. ¶ 86.

The production of a single-cell suspension using Wood’s method is also confirmed by the Shupp Declaration. Specifically, replicating Wood’s Example 1 (¶¶ [0105]-[0112]), Dr. Shupp demonstrates by microscopy that the resulting suspension contained single cells. *See* Shupp Decl. ¶¶ 79, 87.

Thus, Wood discloses “providing a single cell-suspension.” *See* Shupp Decl. ¶¶ 86-87.

c. “...comprising progenitor skin cells...”

Wood discloses that “[c]ells capable of reproduction are then removed from the separated stratum by any means known in the art. ... Cells capable of reproduction within the dermal-epithelial junction include but are not limited to

keratinocyte basal cells, Langerhans cells, fibroblasts and melanocytes.” *See* Wood, ¶ [0057]. These cells capable of reproduction within the dermal-epithelial junction inherently include progenitor skin cells because such cells are inherently present in the dermal epithelial-junction, and no step is taken to remove them or selectively culture some of the cells. *See* Shupp Decl. ¶ 88. Accordingly, Wood discloses single-cell suspensions “comprising progenitor skin cells.” *See* Shupp Decl. ¶ 88.

d. “...in a serum-free physiological solution...”

Wood discloses that “[f]ollowing release of the cells from the tissue sample they are suspended in the nutrient solution.” *See* Wood, ¶ [0057]. “Preferably, the nutrient solution is free of all serum but contains various salts that resemble the substances found in body fluids; this type of solution is often called physiological saline.” *See* Wood, ¶ [0055]. Accordingly, Wood discloses the limitation of “a serum-free physiological solution.” *See* Shupp Decl. ¶ 103.

e. “...in a sterilizable container...”

Wood discloses that the cell suspension may “be aspirated into” a container such as “a syringe.” *See* Wood, ¶ [0097]. The syringe can be part of “set of tools required for cell harvesting.... Preferably, the set of tools are *sterile*. As an example only, the set of tools may include ... [a] syringe.” Wood, ¶ [0092] (emphasis added). Thus, Wood discloses that the single-cell suspension can be

provided “in a sterilizable container.” *See* Shupp Decl. ¶ 103.

f. “...wherein the cells are obtained from the subject’s normal skin tissue...”

Wood discloses obtaining a tissue sample that is “preferably of an autologous nature” which can be “harvested from a patient by means known in the art of tissue grafting.” Wood, ¶ [0048]. By “autologous,” it is meant that “tissue is taken from one area of the body and applied to another area.” Wood, ¶ [0003]. Thus, Wood discloses the limitation that “the cells are obtained from the subject’s normal skin tissue.” *See* Shupp Decl., ¶ 103.

g. “...that has been treated with enzymes so as to release the cells...”

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.” *See* Wood, ¶ [0020]. A POSA understands that by dissociating cohesive pieces of the tissue stratum in a tissue sample, cells are inherently released from the tissue sample. *See* Shupp Decl., ¶ 92. Wood further discloses that “[m]ethods for dissociating cellular layers within the tissues are well known in the field. For example, the dissociating means may be either a physical or chemical disruption means.... Chemical dissociation means might include, for example, digestion with enzymes such as trypsin, dispase, collagenase, trypsin-edta, thermolysin, pronase, hyaluronidase, elastase, papain and pancreatin.” Wood,

¶ [0050]. Further, Woods ‘353 discloses that “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.” Wood, ¶ [0057]. Thus, Wood discloses the limitation that the skin tissue is “treated with enzymes so as to release the cells.” *See* Shupp Decl., ¶¶ 92-93.

h. “...from the dermal-epithelial junction ...”

Wood discloses “[c]ells capable of reproduction are then removed from the separated stratum by any means known in the art. ... Cells capable of reproduction within the *dermal-epithelial junction* include but are not limited to keratinocyte basal cells, Langerhans cells, fibroblasts and melanocytes.” Wood, ¶ [0057] (emphasis added). Thus, Wood discloses the limitation of releasing cells “from the dermal-epithelial junction.” *See* Shupp Decl., ¶ 93.

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

Wood discloses that “the cell population within the suspension is *not expanded* prior to application to the graft site. Rather cellular multiplication is encouraged on the patient rather than in an *in vitro* system.” Wood, ¶ [0061] (emphasis added). *See also* Example 1, ¶¶ [0100]-[0114] wherein no *ex vivo* or *in vitro* expansion was performed. *See* Shupp Decl., ¶ 94. Thus, Wood discloses the limitation that the “skin cells have not been subjected to *ex vivo* or *in vitro* expansion.” *See* Shupp Decl., ¶ 94.

It should be noted that the sole basis for the Examiner's allowance of the '430 Patent was that this feature was allegedly not disclosed in any of the cited prior art. The Examiner clearly overlooked the above-quoted portion of Wood, which is a near verbatim disclosure of this limitation.

- j. **“...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...”**

As discussed in §III(C)(1)(d), a “gas flow” refers to a gas (*e.g.*, propellant gas) which forces the suspension through a flow-controlled spray head (*e.g.*, a nozzle). Wood discloses that the single-cell suspension can be “aspirated into a syringe” and a “nozzle” can be “attached to the syringe for spraying or dripping on to the wound area.” Wood, ¶ [0112]. According to Wood, the nozzle can be “any type of nozzle that transforms liquid into small airborne droplets.” Wood, ¶ [0064]. Accordingly, Wood discloses the use of a flow-controlled spray head to create droplets. *See* Shupp Decl., ¶ 95. However, Wood does not explicitly disclose the use of a “gas flow” to force the suspension through the nozzle.

Wood discloses, however, that “it should not require that the cellular suspension be mixed with a *propellant fluid* that is toxic or detrimental to cells or wound beds.” *See* Wood, ¶ [0064] (emphasis added). A POSA would understand that this teaching to avoid only “toxic or detrimental” propellant fluids, by necessary implication discloses that non-toxic and non-detrimental propellant

fluids may be included. *See* Shupp Decl., ¶ 96. Moreover, a POSA would at once envisage that a “propellant fluid” includes a propellant gas. *See* Shupp Decl., ¶ 96. In addition, Wood discloses the use of a “nozzle” that transforms liquid into small airborne droplets. *See* ¶ [0064]. As discussed *supra* in §III(C)(2)(e), a nozzle is a flow-controlled spray head. Accordingly, it would have been obvious to a POSA to practice Wood by using a flow of propellant gas to force the suspension through the nozzle to create droplets of the suspension. *See* Shupp Decl., ¶ 96.

As such, the limitation, “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,” at the very least, would have been obvious to a POSA in view of Wood. *See* Shupp Decl. ¶¶ 96-103.

k. “...and spraying the droplets onto the wounded area of skin without forming a closed cell sheet ...”

Wood discloses nozzles “for spraying or dripping on to the wound area.” Wood, ¶ [0112]. According to Wood, the nozzle transforms “liquid into small airborne droplets.” Wood, ¶ [0064]. The “cells suitable for grafting back to a patient are collected and dispersed in a solution that is suitable for immediate dispersion over the recipient graft site.” Wood, ¶ [0038]. Because the cells are dispersed in a solution, they inherently fail to form a closed cell sheet, *i.e.*, a collection of adherent cells in the form of a sheet structure. *See* Shupp Decl. ¶ 80.

Indeed, Dr. Shupp's replication of Wood Example 1 demonstrates that no closed cell sheet is formed on the wound. *See* Shupp Decl. ¶ 75. Thus, Wood discloses spraying the droplets onto the wounded area of skin without forming a closed cell sheet. *See* Shupp Decl. ¶ 87.

l. “...so that the single cells are distributed directly and evenly...”

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]. Wood's suspension comprises single cells. *See* § III(E)2(b). Therefore, Wood meets the limitation that the single cells are distributed directly and evenly. *See* Shupp Decl., ¶ 99.

m. “...and the cells regenerate normal skin by *in situ* multiplication to heal the wounded area in the absence of applying a preformed skin graft.”

Wood discloses the cell suspension is “suitable for use in resurfacing and regeneration of damaged tissue” and “is highly suitable for tissue regeneration and grafting techniques.” *See* Wood, ¶¶ [0047], [0060]. In using Wood's cell suspension, “a wound...can be treated quickly by *in situ* multiplication of a limited number of cells.” *See* Wood, ¶ [0060]. 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. Thus, Wood discloses that the cells regenerate normal skin by *in situ* multiplication to heal the wounded area in the absence of applying a preformed skin graft. *See* Shupp Decl., ¶ 100.

As shown above, Wood teaches or suggests every limitation of Claim 1. Claim 1 is therefore invalid as obvious over Wood under 35 U.S.C. §103.

3. Wood Renders Obvious Claim 2

As shown in §III(E)(2), claim 1 is obvious in view of Wood. As shown here, Wood also discloses each element of claim 2, reproduced below:

The method of claim 1 wherein the suspension comprises uncultured cell types in a ratio comparable to that found in normal skin.

Wood discloses producing “a suspension of cells in a ratio to each other comparable with those seen in situ....One possible explanation for this is that in the prior art, culture of the cellular preparation utilises selective culture for keratinocytes, therefore loss of cellular constituents such as fibroblasts and melanocytes occurs whereas the cellular suspension produced from the first aspect of the invention has a cell composition comparable to the in situ cell population.” Wood, ¶¶ [0045], [0062]. Because Wood does not selectively culture specific cell types nor perform *ex vivo* or *in vitro* expansion of the cells, such uncultured cells are necessarily present in the suspension in a ratio comparable to that found in situ

in the normal skin. *See* Shupp Decl. ¶ 128. Claim 2 is therefore invalid as obvious over Wood.

4. Wood Renders Obvious Claim 3

As shown in §§III(E)(2) and III(E)3, claims 1 and 2 are obvious in view of Wood. As shown here, Wood also discloses each element of claim 3, reproduced below:

The method of claim 1 or 2 wherein the cells comprise basal keratinocytes, Langerhans cells, fibroblasts and melanocytes.

Wood discloses the suspension can include “[c]ells capable of reproduction” which “include but are not limited to keratinocyte basal cells, Langerhans cells, fibroblasts and melanocytes.” *See* Wood, ¶ [0057]. “Keratinocyte basal cells” and “basal keratinocytes” are used interchangeably in the art. *See* Shupp Decl. ¶ 131. Thus, Wood discloses that the cells comprise basal keratinocytes, Langerhans cells, fibroblasts, and melanocytes. *See* Shupp Decl. ¶ 131. Claim 3 is therefore invalid as obvious over Wood.

5. Wood Renders Obvious Claim 4

As shown in §§III(E)(2), claim 1 is obvious in view of Wood. As shown here, Wood also discloses each element of claim 4, reproduced below:

The method of claim 1 wherein the cells in the suspension have a

morphology that is similar to the cells in the droplets.

Wood discloses that when using a nozzle, two constraints may apply. “First, it must not subject the cells in solution to shearing forces or pressures that would damage or kill substantial numbers of cells. Second, it should not require that the cellular suspension be mixed with a propellant fluid that is toxic or detrimental to cells or wound beds.” Wood, ¶ [0064]. Thus, a POSA would understand that the nozzle of Wood does not significantly damage the cells. *See Shupp Decl.* ¶ 134. Consequently, a POSA would also understand that the cells in the suspension will have a morphology that is similar to the cells in the droplets since these are viable cells. *See Shupp Decl.* ¶ 134. Indeed, Dr. Shupp’s replication of Wood’s Example 1 demonstrates that before and after spraying through Wood’s apparatus, the morphology of the cells in the suspension is similar to the morphology of the cells in the droplets. *See Shupp Decl.* ¶ 134. Accordingly, claim 4 is also obvious over Wood.

6. Wood Renders Obvious Claim 5

As shown in §§III(E)(2) and III(E)3, claim 2 is obvious over Wood. As shown here, Wood also discloses each element of claim 5, reproduced below:

The method of claim 2 wherein the suspension comprises skin progenitor cells.

As an initial matter, the term “skin progenitor cells” in claim 5 would be

understood by a POSA as identical to the term “progenitor skin cells” in claim 1, *i.e.*, progenitor cells in the skin. *See* Shupp Decl. ¶ 137. Petitioner therefore reserves the right to argue that claim 5 is invalid under 35 U.S.C. 112 (pre-AIA), 4th paragraph, as it fails to further limit the claim upon which it depends.

Nonetheless, as discussed above in §§ III(E)2(c) and III(E)2(h), Wood discloses that the suspension can include “[c]ells capable of reproduction within the dermal-epithelial junction....” Wood, ¶ [0057]. A POSA understands that these cells capable of reproduction within the dermal-epithelial junction necessarily and inherently include progenitor skin cells because progenitor cells are inherently present in the tissue and Wood takes no steps to remove such cells or selectively culture any other cell types. *See* Shupp Decl. ¶ 88. Accordingly, Wood discloses that the suspension comprises skin progenitor cells. Therefore, Claim 5 is also obvious over Wood.

7. Wood Renders Obvious Claim 6

As shown in §III(E)(2), claim 1 is obvious in view of Wood. As shown here, Wood also discloses each element of claim 6, reproduced below:

The method of claim 1 wherein the suspension is filtered to remove large cellular congregates.

Wood discloses that the cell suspension can be filtered using “[a]ny filter capable of separating excessively large cellular congregates from the suspension.”

See Wood, ¶ [0058]. Wood also discloses using a filter with a cutoff ranging from 5-100 cells. *Id.* See also Shupp Decl. ¶¶ 63, and 140-142. Thus, Wood discloses that the suspension is filtered to removed large cellular congregates. See Shupp Decl. ¶¶ 140-142. Claim 7 is therefore obvious over Wood.

8. Wood Renders Obvious Claim 7

As shown in §III(E)(7), claim 6 is obvious over Wood. As shown here, Wood also discloses each element of claim 7, reproduced below:

The method of claim 6, wherein the filter has a cut-off of 5-100 cell congregates.

As an initial matter, there is no antecedent basis for the term “filter” in claim 7. Petitioner reserves all rights to challenge the indefiniteness of the claim on that basis.

Wood discloses that, “[i]n a highly preferred form of the invention, the filter size is between 50µm and 200µm.” Wood, ¶ [0058]. The average size of human skin cells is about 30 µm in diameter and generally ranges from 25-40 µm in diameter. [Ex. 1013]; see also Shupp Decl. ¶ 145. 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 thus, has a cut-off of 2 or 3-cell congregates. See Shupp Decl. ¶ 145. Additionally, a POSA would understand that with a filter size 200 µm, the largest size of a cellular

congregate that will pass through the filter is about 65 cell congregates. *See* Shupp Decl. ¶ 145. Accordingly, the 50-200 µm filter sizes of Wood correspond to a cut-off of about 2-65 cell congregates, which overlaps the range of 5-65 cell congregates of claim 7. *See* Shupp Decl. ¶145.

As the claimed ranges “overlap or lie inside ranges disclosed by” Wood, a *prima facie* case of obviousness exists. *See In re Wertheim*, 541 F.2d 257 (CCPA 1976). Thus, Wood suggests the limitation that the filter has a cut-off of 5-100 cell congregates. *See* Shupp Decl. ¶ 145. Claim 7 is therefore obvious over Wood.

9. Wood Renders Obvious Claim 8

As shown in §III(E)(2), claim 1 is obvious over Wood. As shown here, Wood also discloses each element of claim 8, reproduced below:

The method of claim 1 wherein the enzymes comprise dispase and trypsin.

Wood discloses “digestion with enzymes such as trypsin, dispase” Wood, ¶¶ [0050]-[0051]. Thus, Wood discloses that the enzyme comprises dispase and trypsin. *See* Shupp Decl. ¶ 148. Claim 8 is therefore obvious over Wood.

10. Wood Renders Obvious Claim 9

As shown in §III(E)(2), claim 1 is obvious over Wood. As shown here, Wood also discloses each element of claim 9, reproduced below:

The method of claim 1 wherein the enzymes comprise collagenase.

Wood discloses “digestion with enzymes such as... collagenase...” *See* Wood, ¶¶ [0050]-[0051]. Thus, Wood discloses that the enzyme comprises collagenase. *See* Shupp Decl. ¶ 150. Claim 9 is therefore obvious over Wood.

11. Wood Renders Obvious Claim 10

As shown in §III(E)(2), claim 1 is obvious over Wood. As shown here, Wood also discloses each element of claim 10, reproduced below:

The method of claim 1 wherein the container is a syringe and the suspension is delivered to the outlet of the spray head by continuous force application to the container.

Wood discloses that the single-cell suspension can be “aspirated into a syringe” and a “nozzle” can be “attached to the syringe for spraying or dripping on to the wound area.” *See* Wood, ¶ [0112]. Thus, Wood discloses that the container can be a syringe and the suspension can be delivered to the outlet of the spray head such as a nozzle. *See* Shupp Decl. ¶ 153.

A POSA would understand that a syringe can be operated by applying a force to the plunger for a period of time, until a desired amount of fluid has been expelled from the syringe. *See* Shupp Decl. ¶ 154. A “continuous force” would have been an obvious expedient to assume a steady and even application of the

cells to the wound. *See* Shupp Decl. ¶ 154. Thus, at the very least, Wood suggests that the suspension can be delivered by continuous force application to a syringe. *See* Shupp Decl. ¶ 154. Claim 10 is therefore obvious over Wood.

12. Wood Renders Obvious Claim 11

As shown in §III(E)(2), claim 1 is obvious over Wood. As shown here, Wood also discloses each element of claim 11. Claim 11 of the ‘430 patent is reproduced below:

The method of claim 1 wherein the wounded area is burned.

Wood discloses “a means for the treatment of various skin disorders or diseases” including “burn wounds.” *See* ¶ [0041]. Accordingly, Wood discloses that the wounded area can be burned. *See* Shupp Decl. ¶ 158. Claim 11 is therefore obvious over Wood.

F. Claims 1-11 Are Rendered Obvious by Wood in view of Lyles

As shown in §III(E), Wood teaches, suggests or renders obvious every limitation of claims 1-11. Moreover, as Wood suggests the use of a “nozzle” and “propellant fluid” for use with the cell suspension, a POSA would have been motivated to look to prior art devices for spraying cell suspensions which use propellant gases to produce aerosolized droplets. One such spray device is disclosed in Lyles. As shown below, every limitation of the claims of the ‘430

patent is taught, suggested or rendered obvious by the combined teachings of Wood and Lyles.

Lyles is prior art to the ‘430 patent under 35 U.S.C. §102(b) because it was first published on November 4, 2004—more than one year prior to the September 11, 2006 earliest claimed priority date of the ‘430 patent. Claims 1-11 of the ‘430 patent are invalid as obvious under 35 U.S.C. §103 over Wood in view of Lyles.

1. Wood in view of Lyles renders obvious Claim 1

Each limitation of Claim 1 is met by the combined disclosures of Wood and Lyles, as discussed in detail below.

a. “A method to treat a wounded area of skin on a human subject comprising...”

As demonstrated above in §III(E)(2)(a), Wood discloses the limitation of a “method to treat a wounded area of skin on a human subject comprising...”

b. “...providing a single cell-suspension...”

As demonstrated above in §III(E)(2)(b), Wood discloses the limitation of “providing a single cell-suspension.”

c. “...comprising progenitor skin cells...”

As demonstrated above in §III(E)(2)(c), Wood discloses the limitation of “comprising progenitor skin cells.”

d. “...in a serum-free physiological solution...”

As demonstrated above in §III(E)(2)(d), Wood discloses the limitation of “in a serum-free physiological solution.”

e. “...in a sterilizable container...”

As demonstrated above in §III(E)(2)(e), Wood discloses the limitation of “in a sterilizable container”

f. “...wherein the cells are obtained from the subject’s normal skin tissue...”

As demonstrated above in §III(E)(2)(f), Wood discloses the limitation of “wherein the cells are obtained from the subject’s normal skin tissue.”

g. “...that has been treated with enzymes so as to release the cells...”

As demonstrated above in §III(E)(2)(g), Wood discloses the limitation of “that has been treated with enzymes so as to release the cells.”

h. “...from the dermal-epithelial junction ...”

As demonstrated above in §III(E)(2)(h), Wood discloses the limitation of “from the dermal-epithelial junction.”

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

As demonstrated above in §III(E)(2)(i), Wood discloses the limitation of “wherein the skin cells have not been subjected to *ex vivo* or *in vitro* expansion.”

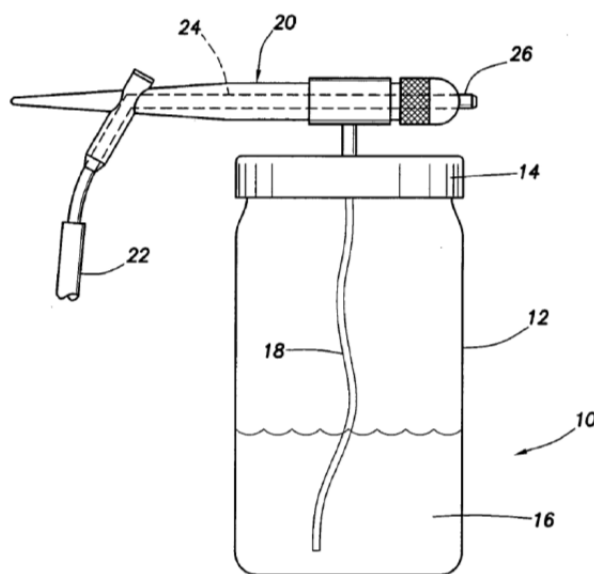
- j. **“...contacting the single-cell suspension of cells with a gas flow at an outlet of the container to create droplets of the suspension at a flow-controlled spray head”**

As discussed above in §III(E)(2)(j), Wood discloses or suggests the use of propellant fluid for contact with the cell suspension. Wood does not, however, expressly disclose a propellant *gas*. A POSA would have been motivated with a reasonable expectation of success to use a gas flow, such as a propellant gas, to produce aerosolized droplets of the suspension at a spray nozzle.

A POSA would have been motivated to employ the “air-jet sprayer” of Lyles to deliver the cell suspension of Wood to the wound site. *See* Lyles at ¶ [0029]. The sprayer of Lyles “uses the velocity of the air flowing through it to create a vacuum that pulls the cell containing media into the air flow resulting in an aerosol spray.” *See* Lyles, ¶ [0029]. Lyles further discloses that “[t]he ‘air’ in the air jet sprayer may be a gas such as carbon dioxide, water vapor, oxygen, nitrogen, argon, helium, neon, or various combinations of any of those gases.” *See* Lyles at ¶ [0031]

Inasmuch as Lyles, like Wood, relates to a “system and method for dispersing living cells onto an area of a subject, lacking normal, healthy skin, such as an open wound surface” (**Lyles, Abstract**), a POSA would have been amply motivated with a reasonable expectation of success to employ the sprayer of Lyles, including the disclosed air flow mechanism, to apply the **cell** suspension of Wood.

See *KSR Int'l Co. v. Teleflex*, 550 U.S. 398, 416 (2007) (“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.”). Moreover, Lyles provides specific motivation to use the disclosed air sprayer to aerosolize a “cell suspension.” **See Lyles at ¶ [0030]**. Lyles’s air sprayer is illustrated in Fig. 1, reproduced below:



Lyles discloses that “to spray cell suspension 16, air from air supply 22 moves through air channel 24 of sprayer tube 20 past the top of hose 18, drawing cell suspension 16 through hose 18 into sprayer tube 20 where it then exits through nozzle 26 as an aerosol spray.” *See Lyles at ¶ [0030]*. Lyles further discloses that the “[q]uantity of cells deposited by the air-jet sprayer may be controlled by...the amount of eluent sprayed, and by the size of the droplet sprayed.” *See Lyles, ¶ [0049]*. Thus, the air-jet sprayer of Lyles contacts the suspension of cells with a gas

flow at an outlet of the container to create droplets of the suspension. *See* Shupp Decl., ¶ 106. Accordingly, 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. A POSA would therefore have naturally looked to the device of Lyles which embodies the “nozzle” and “propellant fluid” features of Wood, and would have understood that Lyles’ devices are suitable for creating droplets of the cell suspension with a gas flow at a flow controlled spray head. *See* Shupp Decl, ¶ 107.

Notably, the Examiner specifically cited Lyles during prosecution as disclosing this limitation (*see* August 25, 2015 Non-Final Rejection, p. 3 and June 1, 2016 Final Rejection, pp. 4-5), and the Applicant did not contest the fact Lyles disclosed a suitable air jet sprayer for a cell suspension, nor did the Applicant overcome this teaching of Lyles (*see* February 23, 2016 Response to Non-Final Rejection, pp. 4-10 and November 11, 2016 Response to Final Rejection, pp. 4-8).

k. “...and spraying the droplets onto the wounded area of skin without forming a closed cell sheet ...”

As demonstrated above in §III(E)(2)(k), Wood discloses the limitation of “spraying the droplets onto the wounded area of skin without forming a closed cell sheet.”

l. “...so that the single cells are distributed directly and

evenly...”

As demonstrated above in §III(E)(2)(l), Wood discloses the limitation of “so that the single cells are distributed directly and evenly.”

m. “...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 demonstrated above in §III(E)(2)(m), Wood discloses the limitation of “the cells regenerate normal skin by *in situ* multiplication to heal the wounded area in the absence of applying a preformed skin graft.” Accordingly, Claim 1 is invalid as obvious under 35 U.S.C. §103 over Wood in view of Lyles.

2. Wood in view of Lyles renders obvious Claim 2

As demonstrated above in §III(E)(3), Wood discloses the limitations of Claim 2. Claim 2 is therefore obvious over Wood in view of Lyles.

3. Wood in view of Lyles renders obvious Claim 3

As demonstrated above in §III(E)(4), Wood discloses the limitations of Claim 3. Claim 3 is therefore obvious over Wood in view of Lyles.

4. Wood in view of Lyles renders obvious Claim 4

As demonstrated above in §III(E)(5), Wood discloses the limitations of Claim 4. Claim 4 is therefore obvious over Wood in view of Lyles.

5. Wood in view of Lyles renders obvious Claim 5

As demonstrated above in §III(E)(6), Wood discloses the limitations of Claim 5. Claim 5 is therefore obvious over Wood in view of Lyles.

6. Wood in view of Lyles renders obvious Claim 6

As demonstrated above in §III(E)(7), Wood discloses the limitations of Claim 6. Claim 6 is therefore obvious over Wood in view of Lyles.

7. Wood in view of Lyles renders obvious Claim 7

As demonstrated above in §III(E)(8), Wood discloses the limitations of Claim 7. Claim 7 is therefore obvious over Wood in view of Lyles.

8. Wood in view of Lyles renders obvious Claim 8

As demonstrated above in §III(E)(9), Wood discloses the limitations of Claim 8. Claim 8 is therefore obvious over Wood in view of Lyles.

9. Wood in view of Lyles renders obvious Claim 9

As demonstrated above in §III(E)(10), Wood discloses the limitations of Claim 9. Claim 9 is therefore obvious over Wood in view of Lyles.

10. Wood in view of Lyles renders obvious Claim 10

As demonstrated above in §III(E)(11), Wood discloses the limitations of Claim 10. Claim 10 is therefore obvious over Wood in view of Lyles.

11. Wood in view of Lyles renders obvious Claim 11

As demonstrated above in §III(E)(12), Wood discloses the limitations of

Claim 11. Claim 11 is therefore obvious over Wood in view of Lyles.

G. Claims 1-11 Are Rendered Obvious by Wood in view of Navarro

Every element of claims 1-11 of the '430 patent is disclosed, taught, suggested or rendered obvious by the combined teachings of Wood in view of Navarro. Navarro is prior art to the '430 patent under 35 U.S.C. §102(b) (pre-AIA) because it published in 2000—more than one year prior to the September 11, 2006 earliest claimed priority date of the '430 patent. Claims 1-11 of the '430 patent are invalid as obvious under 35 U.S.C. §103 over Wood in view of Navarro.

1. Wood in view of Navarro renders obvious Claim 1

Each limitation of Claim 1 is met by the combined disclosure of Wood in view of Navarro, as discussed in detail below.

a. “A method to treat a wounded area of skin on a human subject comprising...”

As demonstrated above in §III(E)(2)(a), Wood discloses the limitation of a “method to treat a wounded area of skin on a human subject comprising...”

b. “...providing a single cell-suspension...”

As demonstrated above in §III(E)(2)(b), Wood discloses the limitation of “providing a single cell-suspension.”

c. “...comprising progenitor skin cells...”

As demonstrated above in §III(E)(2)(c), Wood discloses the limitation of

“comprising progenitor skin cells.”

d. “...in a serum-free physiological solution...”

As demonstrated above in §III(E)(2)(d), Wood discloses the limitation of “in a serum-free physiological solution.”

e. “...in a sterilizable container...”

As demonstrated above in §III(E)(2)(e), Wood discloses the limitation of “in a sterilizable container”

f. “...wherein the cells are obtained from the subject’s normal skin tissue...”

As demonstrated above in §III(E)(2)(f), Wood discloses the limitation of “wherein the cells are obtained from the subject’s normal skin tissue.”

g. “...that has been treated with enzymes so as to release the cells...”

As demonstrated above in §III(E)(2)(g), Wood discloses the limitation of “that has been treated with enzymes so as to release the cells.”

h. “...from the dermal-epithelial junction ...”

As demonstrated above in §III(E)(2)(h), Wood discloses the limitation of “from the dermal-epithelial junction.”

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

As demonstrated above in §III(E)(2)(i), Wood discloses the limitation of “wherein the skin cells have not been subjected to *ex vivo* or *in vitro* expansion.”

j. “...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”

A POSA would have been motivated to employ the “spray devices” of Navarro to deliver Wood’s cell suspension to a wound. Navarro discloses several spray delivery apparatuses “selected on the basis of a uniform cell distribution with high cell viability measurements after the spray.” Navarro, p. 514. One of the spray devices studied in Navarro was an “[a]rtist’s air brush with pressure attached.” *See* Navarro, p. 515, Table 1. A POSA would understand that such a pressurized sprayer necessarily includes a flow of gas contacting the cell suspension to produce a spray. *See* Shupp Decl., ¶ 111. A POSA would have been motivated to Navarro because both references are concerned with spraying cell suspensions onto wounds. *See* Navarro at Abstract (“keratinocytes suspension can potentially treat a variety of epidermal defects...”); pp. 514-515 (“Eight of these wounds (on the right side) were sprayed with a keratinocytes cell suspension.”). *See KSR*, 550 U.S. at 416. Moreover, Navarro discloses that the various spray devices, including the “[a]rtist’s air brush with pressure attached,” produced viable cells when the keratinocyte suspension was sprayed. *See* Navarro, p. 515, Table 1. Accordingly, a

POSA would have understood that all of the spray devices of Navarro, including the air pressurized sprayer of Table 1, would be compatible with Wood's cell suspension and would preserve the morphology of the cells, since the cells were demonstrated to remain viable. As Wood suggests the use of a syringe and "nozzle," as well as a "propellant fluid," a person of ordinary skill would have had a reasonable expectation of success of contacting the cell suspension with a gas flow to produce aerosolized droplets. Accordingly a POSA would have been amply motivated with a reasonable expectation of success to use Navarro's pressurized sprayer. *See* Shupp Decl. ¶ 112.

k. "...and spraying the droplets onto the wounded area of skin without forming a closed cell sheet ..."

As demonstrated above in §III(E)(2)(k), Wood discloses the limitation of "spraying the droplets onto the wounded area of skin without forming a closed cell sheet." Moreover, the '430 patent acknowledges that "Navarro et al. (2000) ... describe the use of single cells suspended in Hartmans's solution and distributed over the wound thus avoiding the sheets." *See* '430 patent, col. 2, lns. 30-32. Accordingly, the '430 patent acknowledges that Navarro also discloses the limitation of spraying the droplets without forming a closed cell sheet.

l. "...so that the single cells are distributed directly and evenly..."

As demonstrated above in §III(E)(2)(l), Wood discloses the limitation of "so

that the single cells are distributed directly and evenly.”

- m. “...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 demonstrated above in §III(E)(2)(m), Wood discloses the limitation of “the cells regenerate normal skin by *in situ* multiplication to heal the wounded area in the absence of applying a preformed skin graft.”

Accordingly, Claim 1 is invalid as obvious under 35 U.S.C. §103 over the combined teachings of Wood in view of Navarro.

2. Wood in view of Navarro renders obvious Claim 2

As demonstrated above in §III(E)(3), Wood discloses the limitations of Claim 2. Claim 2 is therefore obvious over Wood in view of Navarro.

3. Wood in view of Navarro renders obvious Claim 3

As demonstrated above in §III(E)(4), Wood discloses the limitations of Claim 3. Claim 3 is therefore obvious over Wood in view of Navarro.

4. Wood in view of Navarro renders obvious Claim 4

As demonstrated above in §III(E)(5), Wood discloses the limitations of Claim 4. Claim 4 is therefore obvious over Wood in view of Navarro.

5. Wood in view of Navarro renders obvious Claim 5

As demonstrated above in §III(E)(6), Wood discloses the limitations of

Claim 5. Claim 11 is therefore obvious over Wood in view of Navarro.

6. Wood in view of Navarro renders obvious Claim 6

As demonstrated above in §III(E)(7), Wood discloses the limitations of Claim 6. Claim 6 is therefore obvious over Wood in view of Navarro.

7. Wood in view of Navarro renders obvious Claim 7

As demonstrated above in §III(E)(8), Wood discloses the limitations of Claim 7. Claim 7 is therefore obvious over Wood in view of Navarro.

8. Wood in view of Navarro renders obvious Claim 8

As demonstrated above in §III(E)(9), Wood discloses the limitations of Claim 8. Claim 8 is therefore obvious over Wood in view of Navarro.

9. Wood in view of Navarro renders obvious Claim 9

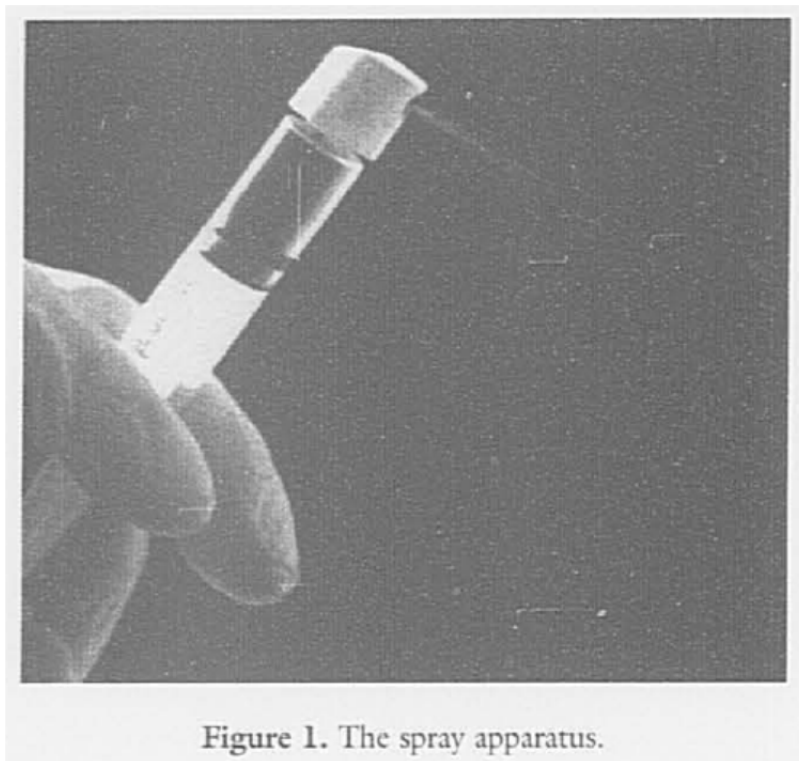
As demonstrated above in §III(E)(10), Wood discloses the limitations of Claim 9. Claim 9 is therefore obvious over Wood in view of Navarro.

10. Wood in view of Navarro renders obvious Claim 10

As demonstrated above in §III(E)(11), Wood discloses the limitations of Claim 10.

Furthermore, Navarro at Fig. 1 (reproduced below) shows a spray apparatus “consisted of a plastic actuator or nozzle (1.5 x 1.5 cm) attached to a 5-mL syringe that was used as a pump. Navarro at p. 514. As shown in Fig. 1, the suspension is

delivered to the outlet of the spray head (plastic actuator or nozzle) by pressing the plunger with a thumb, which is continuous force application to the syringe container. Like Wood, this provides a teaching of continuously spraying the cell suspension through a “nozzle,” which necessarily entails the continuous application of force. Navarro thus evidences that it would be an obvious expedient to use a continuous application of force to provide an even application of the cells over the wound area. *See Shupp Decl.* ¶¶ 111-112.



Claim 10 is therefore obvious over Wood in view of Navarro.

11. Wood in view of Navarro renders obvious Claim 11

As demonstrated above in §III(E)(12), Wood discloses the limitations of

Claim 11. Claim 11 is therefore obvious over Wood in view of Navarro.

H. Claims 1-11 Are Rendered Obvious by Wood in view of Dixon

Every element of claims 1-11 of the '430 patent is disclosed, taught, suggested or rendered obvious by the combined teachings of Wood in view of Dixon. Dixon is prior art to the '430 patent under 35 U.S.C. §102(e) (pre-AIA) because it was filed (by another) prior to the September 11, 2006 earliest claimed priority date of the '430 patent, including as US Provisional No. 60/705,906, filed August 5, 2005 [Ex. 1016] which contains the same disclosure as Dixon. Claims 1-11 of the '430 patent are invalid as obvious under 35 U.S.C. §103 over Wood in view of Dixon.

1. Wood in view of Dixon renders obvious Claim 1

Each limitation of Claim 1 is met by the disclosure of Wood in view of Dixon, as discussed in detail below.

a. “A method to treat a wounded area of skin on a human subject comprising...”

As demonstrated above in §III(E)(2)(a), Wood discloses the limitation of a “method to treat a wounded area of skin on a human subject comprising...”

b. “...providing a single cell-suspension...”

As demonstrated above in §III(E)(2)(b), Wood discloses the limitation of “providing a single cell-suspension.”

c. “...comprising progenitor skin cells...”

As demonstrated above in §III(E)(2)(c), Wood discloses the limitation of “comprising progenitor skin cells.”

d. “...in a serum-free physiological solution...”

As demonstrated above in §III(E)(2)(d), Wood discloses the limitation of “in a serum-free physiological solution.”

e. “...in a sterilizable container...”

As demonstrated above in §III(E)(2)(e), Wood discloses the limitation of “in a sterilizable container.”

f. “...wherein the cells are obtained from the subject’s normal skin tissue...”

As demonstrated above in §III(E)(2)(f), Wood discloses the limitation of “wherein the cells are obtained from the subject’s normal skin tissue.”

g. “...that has been treated with enzymes so as to release the cells...”

As demonstrated above in §III(E)(2)(g), Wood discloses the limitation of “that has been treated with enzymes so as to release the cells.”

h. “...from the dermal-epithelial junction ...”

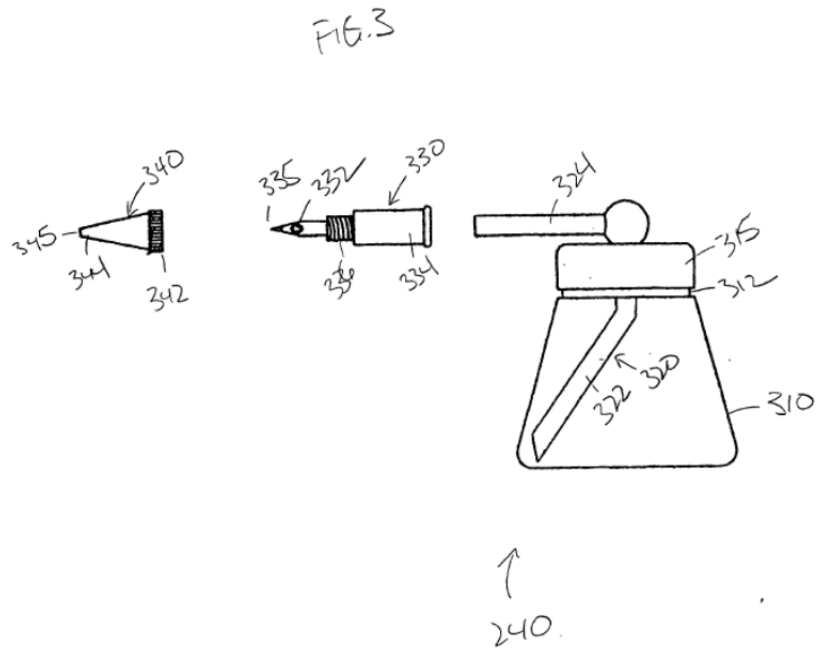
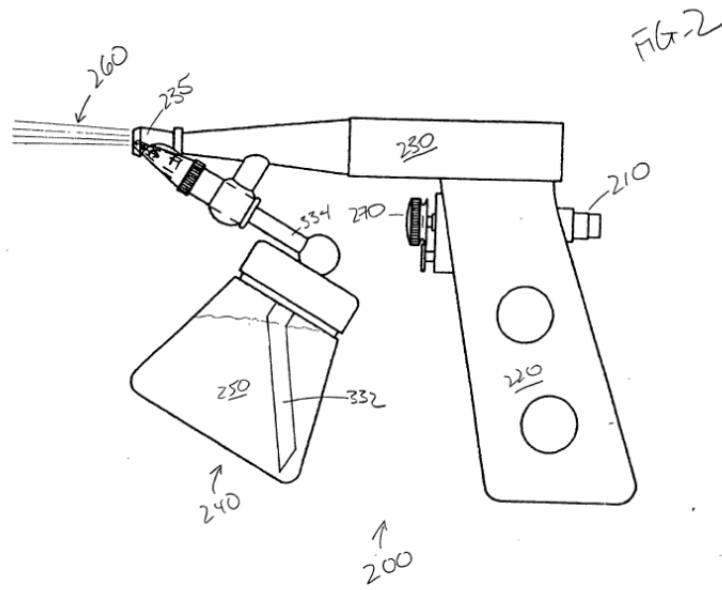
As demonstrated above in §III(E)(2)(h), Wood discloses the limitation of “from the dermal-epithelial junction.”

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

As demonstrated above in §III(E)(2)(i), Wood discloses the limitation of “wherein the skin cells have not been subjected to *ex vivo* or *in vitro* expansion.”

j. “...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”

As Wood suggests the use of a “nozzle” and “propellant fluids” for contact with the cell suspension, a person of ordinary skill would have been motivated to use a propellant gas to aerosolize **droplets** of Wood’s cell suspension at the nozzle of a sprayer. A POSA would naturally have looked to the the “cell spray apparatus” of Dixon to deliver the suspension of Wood to the wound site. *See* Dixon, col. 5, ln. 66 to col. 6, ln. 5. (The step of “[a]pplying therapeutic mixture to recipient surface” may “comprise[] applying a layer of ... donor (autologous) progenitor epidermal/dermal cells...using Applicant’s epidermal/dermal progenitor cell spray apparatus.”). Dixon illustrates the progenitor cell spray apparatus in Figs. 2 and 3, reproduced below:



The cell spray apparatus of Dixon “comprises gas inlet **210**, handle **220**, barrel **230**, reservoir assembly **240**, and trigger mechanism **270**.”). Dixon further discloses that “when trigger mechanism **270** is depressed, pressurized gas is

provided from an external gas source interconnected to gas inlet **210**” and “[a]s that pressurized gas flows past distal portion **235** of barrel **230** and past orifice **345**, the resulting Venturi effect causes Applicant’s thereapeutic mixture **250** to flow outwardly from container **310**, through orifice **345**, and into that pressurized gas to form spray **260**.” *See* Dixon at col. 7, lns. 5-11. Moreover, “[s]pray **260** is propelled outwardly from distal end **235** of barrel **230**” and “then directed onto a recipient surface to deposit a consistent layer of cells thereon.” *See* Dixon at col. 7, lns. 12-14. Additionally, Dixon discloses “the pressure of the one or more gases introduced at inlet **210** must be lower than about 125 psi” and the “[u]se of one or more propellant gases having a pressure greater than about 125 psi may result in damage to the sprayed fetal/donor cells.” *See* Dixon at col. 7, lns. 23-27.

Inasmuch as Dixon, like Wood, relates to a “method to treat a patient having a wound area, such as a burn injury” which “provides a plurality of epidermal cells, and applies that plurality of epidermal cells to the wound area,” (Dixon, Abstract) a POSA would have been amply motivated with a reasonable expectation of success to employ the sprayer of Dixon to apply the cell suspension of Wood. *See KSR*, 550 U.S. at 416. Further, a POSA would have used Dixon’s device which forces fluid through a flow controlled spray head. *See* Shupp Decl. ¶ 118.

- k. “...and spraying the droplets onto the wounded area of skin without forming a closed cell sheet ...”**

As demonstrated above in §III(E)(2)(k), Wood discloses the limitation of “spraying the droplets onto the wounded area of skin without forming a closed cell sheet.”

l. “...so that the single cells are distributed directly and evenly...”

As demonstrated above in §III(E)(2)(l), Wood discloses the limitation of “so that the single cells are distributed directly and evenly.”

m. “...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 demonstrated above in §III(E)(2)(m), Wood discloses the limitation of “the cells regenerate normal skin by *in situ* multiplication to heal the wounded area in the absence of applying a preformed skin graft.”

Accordingly, Claim 1 is invalid as obvious under 35 U.S.C. §103 over the combined teachings of Wood in view of Dixon.

n. Wood in view of Dixon renders obvious Claim 2

As demonstrated above in §III(E)(3), Wood discloses the limitations of Claim 2. Claim 2 is therefore obvious over Wood in view of Dixon.

2. Wood in view of Dixon renders obvious Claim 3

As demonstrated above in §III(E)(4), Wood discloses the limitations of

Claim 3. Claim 2 is therefore obvious over Wood in view of Dixon.

3. Wood in view of Dixon renders obvious Claim 4

As demonstrated above in §III(E)(5), Wood discloses the limitations of Claim 4. Claim 2 is therefore obvious over Wood in view of Dixon.

4. Wood in view of Dixon renders obvious Claim 5

As demonstrated above in §III(E)(6), Wood discloses the limitations of Claim 5. Claim 2 is therefore obvious over Wood in view of Dixon.

5. Wood in view of Dixon renders obvious Claim 6

As demonstrated above in §III(E)(7), Wood discloses the limitations of Claim 6. Claim 6 is therefore obvious over Wood in view of Dixon.

6. Wood in view of Dixon renders obvious Claim 7

As demonstrated above in §III(E)(8), Wood discloses the limitations of Claim 7. Claim 7 is therefore obvious over Wood in view of Dixon.

7. Wood in view of Dixon renders obvious Claim 8

As demonstrated above in §III(E)(9), Wood discloses the limitations of Claim 8. Claim 8 is therefore obvious over Wood in view of Dixon.

8. Wood in view of Dixon renders obvious Claim 9

As demonstrated above in §III(E)(10), Wood discloses the limitations of Claim 9. Claim 9 is therefore obvious over Wood in view of Dixon.

9. Wood in view of Dixon renders obvious Claim 10

As demonstrated above in §III(E)(11), Wood discloses the limitations of Claim 10. Claim 10 is therefore obvious over Wood in view of Dixon.

10. Wood in view of Dixon renders obvious Claim 11

As demonstrated above in §III(E)(12), Wood discloses the limitations of Claim 11. Claim 11 is therefore obvious over Wood in view of Dixon.

I. Claims 1-11 Are Rendered Obvious by Wood in view of Marshall

Every element of claims 1-11 of the ‘430 patent is disclosed, taught, suggested or rendered obvious by prior art reference Wood in view of Marshall. Marshall is prior art to the ‘430 patent under 35 U.S.C. §102(b) (pre-AIA) because it issued on November 12, 2002—more than one year prior to the September 11, 2006 earliest claimed priority date of the ‘430 patent. Claims 1-11 of the ‘430 patent are invalid as obvious under 35 U.S.C. §103 over Wood in view of Marshall.

1. Wood in view of Marshall renders obvious Claim 1

Each limitation of Claim 1 is met by Wood in view of Marshall, as discussed in detail below.

a. “A method to treat a wounded area of skin on a human subject comprising...”

As demonstrated above in §III(E)(2)(a), Wood discloses the limitation of a

“method to treat a wounded area of skin on a human subject comprising...”

b. “...providing a single cell-suspension...”

As demonstrated above in §III(E)(2)(b), Wood discloses the limitation of “providing a single cell-suspension.”

c. “...comprising progenitor skin cells...”

As demonstrated above in §III(E)(2)(c), Wood discloses the limitation of “comprising progenitor skin cells.”

d. “...in a serum-free physiological solution...”

As demonstrated above in §III(E)(2)(d), Wood discloses the limitation of “in a serum-free physiological solution.”

e. “...in a sterilizable container...”

As demonstrated above in §III(E)(2)(e), Wood discloses the limitation of “in a sterilizable container”

f. “...wherein the cells are obtained from the subject’s normal skin tissue...”

As demonstrated above in §III(E)(2)(f), Wood discloses the limitation of “wherein the cells are obtained from the subject’s normal skin tissue.”

g. “...that has been treated with enzymes so as to release the cells...”

As demonstrated above in §III(E)(2)(g), Wood discloses the limitation of

“that has been treated with enzymes so as to release the cells.”

h. “...from the dermal-epithelial junction ...”

As demonstrated above in §III(E)(2)(h), Wood discloses the limitation of “from the dermal-epithelial junction.”

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

As demonstrated above in §III(E)(2)(i), Wood discloses the limitation of “wherein the skin cells have not been subjected to *ex vivo* or *in vitro* expansion.”

j. “...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”

As Wood suggests the use of a “nozzle” and “propellant fluids” for the cell suspension, a POSA would have had been motivated with a reasonable expectation of success to use a spray nozzle with a gas propellant to produce aerosolized droplets. A POSA would therefore have been motivated to employ the “Spraying Devices” of Marshall to deliver the suspension of Wood to the wound site since those devices use a gas propellant to aerosolize a cell suspension at a spray nozzle. *See* Marshall, col. 8, lns. 38-39. Marshall “provides a method of, in a mammal, delivering cells to a tissue surface, comprising: spraying a suspension of cells onto the surface in an amount effective to secure a colonization promoting effective

amount of the cells on the surface; and maintaining or growing the cells on the surface” and “[p]referably, the cells are sprayed with liquid flows less than 3.0 ml/min.” *See* col. 3, lns. 22-27.

Marshall discloses contacting a gas flow with the cell suspension. *See* col. 7, ln. 50 to col. 8, ln. 29. In some embodiments, “the cell suspension alone [is] sprayed.” *See* col. 8, lns. 38-39. In one embodiment, a spray device “has a central gas outlet, and two ring outlets arrayed around the gas outlet...to help shape and merge the output streams.” *See* col. 8, lns. 2-3. This device “can further be modified to provide a third outlet, such as a ring outlet for the cell suspension.” *See* col. 8, lns. 8-10. Moreover, “[t]he cell suspension can be delivered from the same spraying device that delivers the two component fibrin system.” *See* col. 8, lns. 40-42. Additionally, Marshall discloses that “[g]as flows, when used are preferably 500 ml/min to 800 ml/min” and that “[a]n adjacent gas flow tends to draw in the liquid stream, and disperse the stream into smaller droplets creating a ‘dispersion spray.’” *See* col. 8, lns. 29-32. Moreover, “[w]hen cell suspensions alone are sprayed the above described low liquid flow rates are preferably used.” *See* col. 8, lns. 38-39, emphasis added.

Inasmuch as Marshall, like Wood, relates to a method comprising “spraying a suspension of the cells onto the coated target surface,” a POSA would have been

amply motivated with a reasonable expectation of success to employ the pressurized sprayer of Marshall, to apply the cell suspension of Wood because Marshall teaches that cell suspensions can be sprayed with such a device. *See KSR*, 550 U.S. at 416.

k. “...and spraying the droplets onto the wounded area of skin without forming a closed cell sheet ...”

As demonstrated above in §III(E)(2)(k), Wood discloses the limitation of “spraying the droplets onto the wounded area of skin without forming a closed cell sheet.”

l. “...so that the single cells are distributed directly and evenly...”

As demonstrated above in §III(E)(2)(l), Wood discloses the limitation of “so that the single cells are distributed directly and evenly.”

m. “...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 demonstrated above in §III(E)(2)(m), Wood discloses the limitation of “the cells regenerate normal skin by *in situ* multiplication to heal the wounded area in the absence of applying a preformed skin graft.”

2. Wood in view of Marshall renders obvious Claim 2

As demonstrated above in §III(E)(3), Wood discloses the limitations of

Claim 2. Claim 2 is therefore obvious over Wood in view of Marshall.

3. Wood in view of Marshall renders obvious Claim 3

As demonstrated above in §III(E)(4), discloses the limitations of Claim 3.

Claim 3 is therefore obvious over Wood in view of Marshall.

4. Wood in view of Marshall renders obvious Claim 4

As demonstrated above in §III(E)(5), Wood discloses the limitations of Claim 4. Claim 4 is therefore obvious over Wood in view of Marshall.

5. Wood in view of Marshall renders obvious Claim 5

As demonstrated above in §III(E)(6), Wood discloses the limitations of Claim 5. Claim 5 is therefore obvious over Wood in view of Marshall.

6. Wood in view of Marshall renders obvious Claim 6

As demonstrated above in §III(E)(7), Wood discloses the limitations of Claim 6. Claim 6 is therefore obvious over Wood in view of Marshall.

7. Wood in view of Marshall renders obvious Claim 7

As demonstrated above in §III(E)(8), discloses the limitations of Claim 7. Claim 7 is therefore obvious over Wood in view of Marshall.

8. Wood in view of Marshall renders obvious Claim 8

As demonstrated above in §III(E)(9), Wood discloses the limitations of Claim 8. Claim 8 is therefore obvious over Wood in view of Marshall.

9. Wood in view of Marshall renders obvious Claim 9

As demonstrated above in §III(E)(10), Wood discloses the limitations of Claim 9. Claim 9 is therefore obvious over Wood in view of Marshall.

10. Wood in view of Marshall renders obvious Claim 10

As demonstrated above in §III(E)(11), Wood discloses the limitations of Claim 10. Claim 10 is therefore obvious over Wood in view of Marshall.

11. Wood in view of Marshall renders obvious Claim 11

As demonstrated above in §III(E)(12), Wood discloses the limitations of Claim 11. Claim 11 is therefore obvious over Wood in view of Marshall.

IV. CONCLUSION

For the foregoing reasons, the Petitioner respectfully submits that the evidence presented in this petition establishes a reasonable likelihood that Petitioner will prevail in establishing claims 1-11 of the '430 patent are unpatentable, and requests that Trial be instituted to cancel these claims.

Respectfully submitted,
GREENBERG TRAURIG, LLP

Date: April 4, 2017

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CERTIFICATION UNDER 37 C.F.R. §42.24(a)(1)(i)

Petitioner certifies that the word count for this *inter partes* review petition is under 14,000 words as determined according to 37 C.F.R. §42.24(a)(1). The exact word count, as determined by the word-processing system used to prepare the petition is 13,924.

Respectfully submitted,
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**PETITION FOR INTER PARTES REVIEW
OF U.S. PATENT NO. 9,610,430 (Claims 1-11)**

**Attachment A:
Proof of Service of the Petition**

CERTIFICATE OF SERVICE

I hereby certify that on this 4th day of April, 2017, a copy of this Petition, including all attachments, appendices and exhibits, has been served in its entirety via United States Postal Service Priority Mail Express on the following correspondence address for patent owner:

Renovacare Sciences Corp.
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Respectfully submitted,
GREENBERG TRAURIG, LLP

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PETITION FOR INTER PARTES REVIEW
OF U.S. PATENT NO. 9,610,430 (Claims 1-11)

Attachment B:

List of Evidence and Exhibits Relied Upon in Petition

Exhibit #	Description
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	Curriculum Vitae 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, http://www.stedmanonline.com/popup.aspx?aid=5188026
1012	Stedman’s Medical Dictionary, <i>in vitro</i> definition, http://www.stedmanonline.com/popup.aspx?aid=5200863
1013	https://en.wikipedia.org/wiki/Human_skin article
1014	https://en.wikipedia.org/wiki/Nozzle article
1015	https://en.wikipedia.org/wiki/Airbrush article
1016	US Provisional Application No. 60/705,906 filed August 5, 2005