2023-2054

United States Court of Appeals for the Federal Circuit

RESTEM, LLC,

Appellant,

– v. –

JADI CELL, LLC,

Appellee.

On Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2021-01535

BRIEF FOR APPELLANT

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UNITED STATES PATENT NO. 9,803,176

CLAIM 1

1. An isolated cell prepared by a process comprising:

placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate; and

culturing the subepithelial layer such that the isolated cell from the subepithelial layer is capable of self-renewal and culture expansion,

wherein the isolated cell expresses at least three cell markers selected from the group consisting of CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, or CD105, and

wherein the isolated cell does not express NANOG and at least five cell markers selected from the group consisting of CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 2023-2054

Short Case Caption Restem, LLC v. Jadi Cell, LLC

Filing Party/Entity Restem, LLC

Instructions:

1. Complete each section of the form and select none or N/A if appropriate.
2. Please enter only one item per box; attach additional pages as needed, and check the box to indicate such pages are attached.
3. In answering Sections 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance.
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I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 09/29/2023

Signature: /s/ Kevin C. Hooper

Name: Kevin C. Hooper

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☑ None/Not Applicable
Restem, LLC		

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

BRYAN CAVE LEIGHTON PAISNER LLP	Kevin C. Hooper	Ethan R. Fitzpatrick
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5. Related Cases. Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

☐ Yes (file separate notice; see below) ☑ No ☐ N/A (amicus/movant)

If yes, concurrently file a separate Notice of Related Case Information that complies with Fed. Cir. R. 47.5(b). **Please do not duplicate information.** This separate Notice must only be filed with the first Certificate of Interest or, subsequently, if information changes during the pendency of the appeal. Fed. Cir. R. 47.5(b).

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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STATEMENT OF RELATED CASES

No other appeal in or from the proceedings below was previously brought in this or any other appellate court. This is an appeal from the Final Written Decision ("FWD") of the U.S. Patent and Trademark Office's ("PTO's") Patent Trial and Appeals Board ("Board") in *inter partes* review ("IPR") number IPR2021-01535 in which the Board determined that Petitioner did not demonstrate by a preponderance of the evidence that the challenged claims (1 to 15) of U.S. Patent No. 9,803,176 ("the '176 patent") were unpatentable. The '176 patent is the parent of several applications currently pending in the United States patent office: U.S. Ser. Nos. 17/322,672, 17/559,539, 17/559,545, 17/559,583.

Restem is not aware of any other proceeding that may affect, or be affected by, a decision in this consolidated appeal.

STATEMENT OF JURISDICTION

The Board had jurisdiction over this *inter partes* review proceeding under 35 U.S.C. §6. On April 18, 2023, the Board issued a Final Written Decision in the underlying proceeding pursuant to 35 U.S.C. §318(a) and 37 C.F.R. §42.73. Restem timely filed and served its Notice of Appeal on June 16, 2023, pursuant to 35 U.S.C. §142. This Court has jurisdiction under 28 U.S.C. §1295(a)(4)(A) and 35 U.S.C. §141(c). Appellants have standing to appeal the Final Written Decision because it has concrete plans that raise a substantial risk of infringement. *Gen. Elec. Co. v. Raytheon Techs. Corp.*, 983 F.3d 1334, 1341 (Fed. Cir. 2020); *see also LKQ Corp. v. GM Glob. Tech. Operations LLC*, No. 2021-2348, 2023 WL 328228, at *2 (Fed. Cir. Jan. 20, 2023). Since 2007 Appellant (and its predecessor entities) spent over $15 million on research and clinical development of umbilical cord lining stem cells. Restem's research and development includes, *inter alia*, studies to test and develop methods for isolating cells from umbilical cord, characterizing the isolated cells to meet regulatory requirements (*e.g.*, measuring telomeres, testing for genetic aberrations, determining contents of secreted products), maintaining cell banks, and testing its isolated cells in clinical trials. Restem currently has four investigational new drug (IND) clinical studies ongoing, including three that are about to begin Phase II. Restem also has 20 ongoing "compassionate use" studies for treatment of, *inter alia*, pulmonary fibrosis and autoimmune diseases. Restem's umbilical cord

lining stem cells used in all of its research and development activities include cells derived from the subepithelial layer of umbilical cord via an explant procedure. Restem's cells are capable of self-renewal and culture expansion, can differentiate into adipocytes, osteocytes, cardiomyocytes, and chondrocytes, and can produce exosomes. Moreover, Restem's cells express, *inter alia*, CD105, CD90, CD73, and CD44, and do not express, *inter alia*, CD34, CD45, CD19, and HLA-DR. Thus, while Restem does not concede infringement, Restem's activities raise a substantial risk of infringement. *Gen. Elec.,* 983 F.3d at 1341. The amicus brief filed in support of the Final Written Decision, which cites its October 24, 2022 Form 8-K filing with the U.S. Security and Exchange Committee (SEC) is evidence that Jadi Cell's licensee continues to be aggressive in protecting its exclusivity with respect to the licensed technology of the '176 patent. The exclusive licensee's pattern of conduct further raises the risk that an infringement action will be filed against Restem.

STATEMENT OF THE ISSUES

1. Whether the Board applied an incorrect claim construction to the product-by-process claims, where the Board implicitly construed the claims as requiring several additional process steps not recited in the claims.

2. Whether the Board incorrectly determined that the prior art does not inherently anticipate or render obvious the product-by-process claims where the Board found that the prior art teaches the only two steps recited in the claim as the process for producing the product.

STATEMENT OF THE CASE

This is an appeal from a Final Written Decision (FWD) in which the Board found that the prior art teaches the same process steps recited in the product-by-process claims, yet found that the prior art does not anticipate or render obvious the claimed product made by that process. The Board's FWD raises issues at the intersection of the law of product-by-process claims and inherency.

The claims at issue are simply directed to an isolated cell produced by a two-step process, wherein the produced isolated cell has a specified marker pattern. In the FWD, the Board found that the claimed isolated cell is produced as a result of the two claimed process steps. The Board also ***found that the prior art teaches an isolated cell produced by the same two-step process***. Nevertheless, the Board held that the prior art does not anticipate or render obvious the claims. The Board's conclusion relies upon two fundamental errors.

First, although, in its claim construction section, the Board correctly construed the claims as covering cells produced by performing the two process steps expressly recited in the claims, when evaluating the prior art, the Board implicitly construed the claims as further requiring additional ***unrecited*** process steps. Specifically, when addressing the disputed claim terms, the Board performed a thorough claim construction analysis in which it concluded the claims recite cells produced by the expressly-recited two-step process, without requiring any other

conditions or steps (*i.e.*, a product made by the claimed process). In so doing, the Board explicitly rejected Jadi Cell's arguments that the claims should be interpreted to include additional unrecited process steps to achieve the claimed "isolated cell." Indeed, the Board provided an eight-page analysis ***rejecting*** Jadi Cell's proposed claim construction requiring additional steps comprising isolation of subepithelial layer (SL) and orienting the SL interior side down. Appx17-24.

Nevertheless, the Board then proceeded to conclude that the prior art did not anticipate or render obvious the claims ***for not disclosing those very same unrecited additional steps***. In particular, the Board determined that the prior art would not produce the claimed cells because the prior art "differ[s] from at least the interior-down embodiment disclosed in the '176 patent." *See, e.g.*, Appx39, Appx61. Moreover, the Board also determined that the prior art failed to teach additional unrecited and unspecified "factors" and "conditions" without any meaningful analysis or explanation. Thus, the Board implicitly construed the claimed process as requiring additional steps, as well as "factors" and "conditions," none of which are recited in the claims. As this court has repeatedly cautioned, it is impermissible to read limitations into the claims without "expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *Continental Circuits LLC v. Intel Corp.*, 915 F.3d 788, 796–97 (Fed. Cir. 2019) (internal quotations omitted). The Board's "reading in" is particularly problematic here, given these are product-

by-process claims, and it is well-settled that the expressly-recited steps define the scope of the claimed product. Critically, the Board's improper implicit constructions infect all of its reasoning for upholding the challenged claims, and, therefore, the FWD should be reversed for this reason alone.

Second, the Board applied an improper standard for inherency of product-by-process claims. The Board found that the prior art teaches an isolated cell made by the same two-step process as the claims. Appx32-34, Appx59, Appx68. As both the claims and the specification make clear, this two-step process results in cells having the marker patterns specified in the claims. *See, e.g.,* Appx103, claim 1, Appx94, 1:33-41, Appx97, 7:67-8:6, Appx97, 8:3-6. Indeed, this is the very essence of a product-by-process claim, namely: the claimed product (an isolated cell with certain marker patterns) is defined by the process recited in the claim (the two-step process). Thus, it is indisputable that performing the prior art two-step processes will always result in cells having the specified marker patterns recited in the claims. Indeed, to say otherwise would mean that the ***claimed process does not actually result in the claimed product***.

The Board found, however, that this was not enough to establish inherency. Rather, the Board further required Restem to prove "that the marker expression profile is *only* dependent on the process used to produce the claimed cells." Appx40, Appx63, Appx70 (emphasis in original). In other words, the Board required Restem

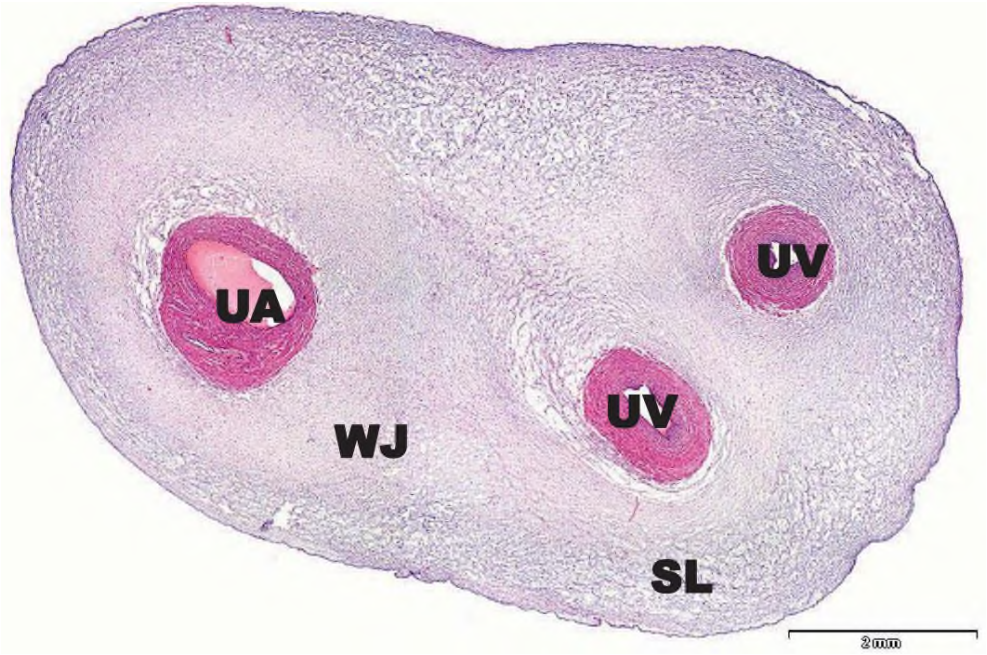
to prove that there were no other steps or conditions—***not recited in the claims***—that affect the marker expression profile of the cells. Thus, the Board effectively required Restem to establish that the ***claimed*** two-step process actually produces the claimed product. This is not the correct standard for inherency. To the contrary, it is well established that "[a] limitation is inherent if it is the 'natural result flowing from' the prior art's explicit disclosure." *Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023) quoting *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003). Here, because the prior art teaches the claimed two-step process, it is indisputable that the natural result flowing from the prior art's process will be the claimed cells having the specified marker patterns. The Board's application of an improper requirement to prove inherency was legal error, and, for this additional reason, its patentability determinations should be reversed.

STATEMENT OF THE FACTS

A. Overview of the Alleged Invention

The '176 Patent is directed to an isolated cell having specified cell surface markers obtained from the subepithelial layer (SL) of umbilical cord tissue, and methods of obtaining and culturing such cells. *See, e.g.*, Appx78, Abstract, Appx94 1:31-50. Figure 1 of the '176 patent is reproduced below showing a cross section of an umbilical cord with various anatomical parts labeled: umbilical artery (UA),

umbilical vein (UV), Wharton's Jelly (WJ), and subepithelial layer (SL). Appx97, 7:62-65.



At the priority date of the '176 patent, it was well known that cells could be obtained from umbilical cord tissue and that such cells comprised, *inter alia*, stem cells, progenitor cells, and differentiated cells. Appx1716-1717. Such cells were known to express (or not express) many different cell markers. *Id*. Methods for isolating sub-populations of these cells, such as mesenchymal stem cells (MSCs), from umbilical cord tissue were also well known at the priority date of the '176 patent. *Id*. Such methods included contacting umbilical cord explants with a tissue culture substrate, which allows MSCs to be isolated *via* migration and adhesion to the substrate (*i.e.*, using an "explant" procedure). Appx1716-1717, Appx1711. It

was also well known that cells from all the tissues of the umbilical cord could be isolated by this procedure, and that such cells have potential value, *inter alia*, as a source of stem cells for both research and medicine and for the ability to differentiate into multiple cell types. Appx1703-1716.

As explained by the '176 Patent, the claimed isolated cell is obtained from the SL of a mammalian umbilical cord using any one of a "variety of techniques" so long as the technique "allows such extraction without significant damage to the cells." Appx97, 8:1-2, 8:34-38. The specification discloses that the methods of obtaining stem cells from the SL are broad, including the steps of placing a SL from the umbilical cord in direct contact with a substrate and culturing the SL. The '176 patent explains that the SL "can be cultured in any media capable of producing explants therefrom" (Appx94, 2:21-22) using "any substrate capable of deriving explants" (Appx94, 2:29-30), and using "various culturing conditions" (Appx94, 2:4-42), including e.g., normoxic/hypoxic conditions, with/without use of enzymes, culturing for any period of time "sufficient to produce primary cultures" (Appx98, 9:16-18), and employing one or more of various growth factors (Appx98, 10:7-12).

Importantly, the markers present on the cells of the '176 patent were not selected by the inventor, and instead are simply imparted by the process of isolating the cell. The '176 patent discloses that the "[i]solated cells from the SL can have a variety of characteristic markers that distinguish them from cell[s] previously

isolated from umbilical cord samples." 'Appx97, 7:65-67. Thus, the '176 Patent is directed to, *inter alia*, cells obtained from the SL of umbilical cord that are isolated in a manner that selects for cells having certain markers. Appx1719-1722.

B. The Challenged Claims

The Challenged Claims recite:

> 1. An isolated cell prepared by a process comprising:
> placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate; and
> culturing the subepithelial layer such that the isolated cell from the subepithelial layer is capable of self-renewal and culture expansion,
> wherein the isolated cell expresses at least three cell markers selected from the group consisting of CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, or CD105, and
> wherein the isolated cell does not express NANOG and at least five cell markers selected from the group consisting of CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR.

Certain of the dependent Challenged Claims recite additional characteristics of the claimed isolated cell (see claims 2-8), and certain other Challenged Claims are directed to a method of culturing (claim 9) and a culture of differentiated cells derived from the isolated cell (claims 10-15).

Notably, the claims do not recite newly discovered umbilical cord tissue from which cells could be obtained, do not recite new methods for obtaining cells from umbilical cord tissue, and do not recite new tissue culture techniques for propagating or differentiating cells. Appx1717-1719. Rather, the claims merely recite "an isolated cell" prepared by a well-known process of contacting the tissue of a

mammalian umbilical cord to a tissue culture substrate to obtain isolated cells having a particular marker pattern. *Id*. Moreover, it is undisputed that the recited markers of the claims were not *a priori* selected by the inventor to be expressed by the isolated cell. Appx489-490. To the contrary, the recited markers are simply characteristics of the isolated cell at an undefined point in time that are produced when the two recited steps in the claim are carried out. *See* Appx97, 7:65-8:6, Appx489-490. The purported "novelty" of the Challenged Claims is merely in the identification of a cell obtained by contacting the subepithelial layer of a mammalian umbilical cord to a substrate and culturing to obtain a cell capable of self renewal and culture expansion, which can allegedly be used to "treat a wide range of medical conditions." Appx97, 7:23-25, Appx1717-1718.

But as the Board correctly found, producing a cell by contacting the SL with a substrate and culturing the SL to produce cells capable of self-renewal and culture expansion was well known in the prior art. Appx32-34, Appx59, Appx67-68. Indeed, the Board correctly determined that each of Majore, Phan, and Kita all disclose producing a cell from the SL capable of self-renewal and culture expansion according to the same process steps as the Challenged Claims. *Id*.

C. The Cited Art

1. Majore

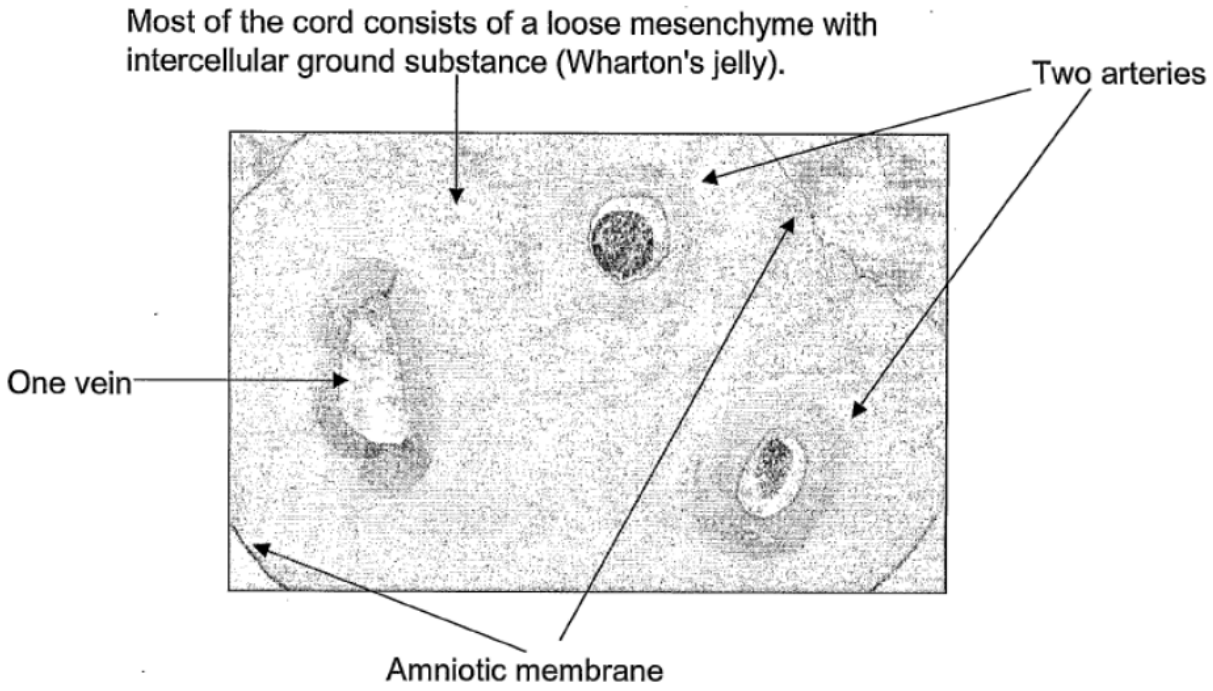
Majore[1] discloses isolating mesenchymal stem cells (MSCs) from human umbilical cord tissue. Appx1931. Majore discloses a protocol wherein whole umbilical cord tissue (including SL) is minced and contacted with a growth substrate, followed by culturing to produce highly proliferative MSCs. Appx1932. Majore also discloses that the MSCs produced according to its protocol express CD73, CD90, CD44, and CD105, and do not express CD45 and CD34. Appx1937 (Table 2).

2. Phan

Phan[2] discloses a method for isolating "stem/progenitor cells from the amniotic membrane of umbilical cord" comprising "separating the amniotic membrane from the other components of the umbilical cord *in vitro*, culturing the amniotic membrane tissue under conditions allowing cell proliferation, and isolating the stem/progenitor cells from the tissue cultures." Appx2168. Figure 16 of Phan, reproduced below, is an image of an umbilical cord cross-section showing the amniotic membrane tissue (comprising the SL) from which its cells were derived.

[1] Ingrida Majore, *et al.*, Growth and Differentiation Properties of Mesenchymal Stromal Cell Populations Derived from Whole Human Umbilical Cord, STEM CELL REV. AND REP. 7:17–31 (2011) (Appx1931-1945, "Majore").

[2] Toan-Thang Phan and Ivor Jiun Lim, WO 2006/019357 Al, published February 23, 2006 (Appx2167-2280, "Phan").

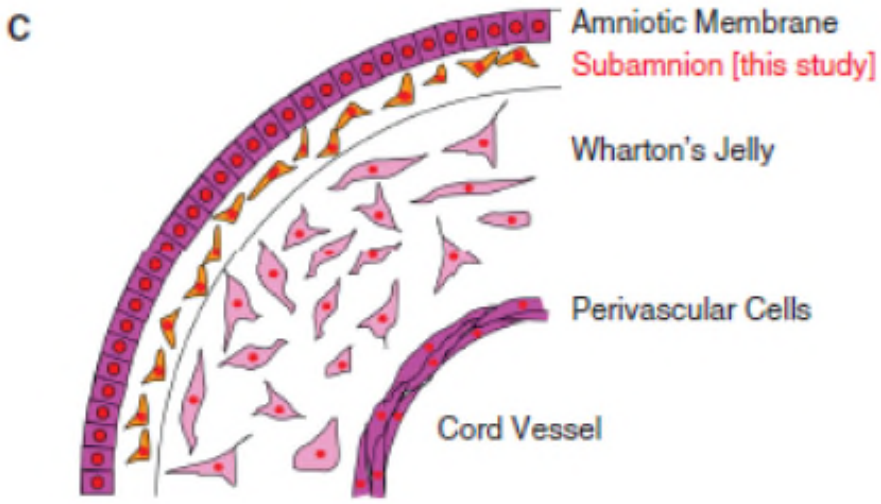


Phan at Fig 16 (Appx2230); para [0033] (Appx2175).

3. Kita

Kita[3] discloses a protocol to "isolate adult SCs from the cord lining membrane (subamniotic region of the umbilical cord), and characterize the isolated cells as a novel source for cell-based therapeutic approaches." Appx1920. According to Kita's protocol, Wharton's jelly inside the cord was dissected away, and the remaining tissue comprising SL was cultured in growth medium. *Id*. Figure 1C of Kita, reproduced below, is a diagram showing the umbilical cord tissue from which its cells were derived.

[3] Katsuhiro Kita, *et al.*, Isolation and Characterization of Mesenchymal Stem Cells From the Sub-Amniotic Human Umbilical Cord Lining Membrane, STEM CELLS AND DEV. 19(4):491–501 (2009) (Appx1919-1930, "Kita").



Appx1921.

D. The Proceedings Below

On September 29, 2021, Restem filed an IPR petition challenging claims 1-15 of the '176 patent. Restem challenged these claims on a variety of anticipation and obviousness grounds based on three primary references (Majore, Phan, and Kita) and five secondary references (Mistry, Pierantozzi, Rojewski, Meiron, and Riekstina). Appx207-274. Among other things, Restem argued that because each of Majore, Phan, and Kita disclose obtaining a cell according to the same steps of the challenged product-by-process claims, Majore, Phan, and Kita each necessarily produce a cell having the markers according to the Challenged Claims. Appx226, 228-231, 250, 262-263. In other words, because the markers of the Challenged Claims were an inherent feature of cells produced according to the expressly-recited two-step process, cells having those same markers would naturally be produced by

Majore, Phan, and Kita because they each produce a cell according to the same two-step process. *Id*. Restem further argued that the secondary references disclosed that cells of the same type as produced by Majore, Phan, and Kita (*i.e.*, MSCs) were known to express or not express a variety of cell markers, including all the markers recited in the Challenged Claims. Appx238-243, Appx246-255, Appx263-270.

On January 31, 2022, Jadi Cell filed a preliminary response, arguing, *inter alia*, that the processes disclosed by Majore, Phan, and Kita do not produce cells having the recited markers because the Challenged Claims require extra (unrecited) process steps disclosed by the specification in order to produce the claimed "isolated cell." *See, e.g.*, Appx322-323, Appx325, Appx348, Appx359. Specifically, Jadi Cell argued that the process steps of the Challenged Claims should be construed to include the extra steps of removing Wharton's Jelly and placing the SL interior side down in contact with a substrate. Appx310. Jadi Cell asserted that it was these additional process step that were actually responsible for the marker pattern recited in the claims. *See* Appx310-311, Appx322-323, Appx325, Appx348, Appx359.

1. The Board Institutes the Appealed IPR

The Board instituted the IPR on all Challenged Claims and on all grounds raised in the petition. Appx417. The Board began by addressing the parties' differing interpretation of "an isolated cell," ultimately adopting a definition consistent with Jadi Cell's proposed definition as "one or more cells isolated from

the subepithelial layer of a mammalian umbilical cord." Appx383. The Board also adopted Jadi Cell's proposed definition of "subepithelial layer" as meaning "the layer of tissue in umbilical cord that is located between—and distinct from—the amniotic membrane and Wharton's Jelly." Appx384. The Board then turned to the Parties' arguments concerning the prior art. Among other things, the Board:

- Agreed there was "a reasonable likelihood that Majore's explant method of dissecting umbilical cord, culturing cells, and growing adherent cells would have produced (or did produce) at least one cell with the recited limitations." Appx391;

- Credited Petitioner's expert testimony that "the cells obtained by Majore's protocol necessarily and inevitably comprise the same cells produced by the process steps of claim 1[A] and 1[B] and that the skilled artisan would have understood that the marker expression pattern would be identical for those cells." Appx391 (internal quotation omitted).

- Agreed there was "a reasonable likelihood that Phan's disclosed method of dissecting umbilical cord, culturing cells, and growing adherent cells would have produced (or did produce) at least one cell with the limitations of claim 1." Appx406.

- Credited Petitioner's expert testimony that "the cells produced by Phan would include the same [cell] produced by the '176 patent." Appx406.

- Agreed there was a reasonable likelihood that Kita's "disclosed method of dissecting umbilical cord, culturing cells, and growing adherent cells would have produced (or did produce) at least one cell with the limitations of claim 1." Appx410.

- Credited Petitioner's expert testimony that "the cells produced by Kita would include the same [cell] produced by the '176 patent." Appx410-411.

2. Jadi Cell's Patent Owner Response and Restem's Reply Thereto

Jadi Cell filed its response on July 13, 2022. Appx466. In an attempt to overcome the prior art, Jadi Cell threw the proverbial kitchen-sink at the Board, which included arguing new claims constructions (Appx481-488), arguing that all the elements of the claims were missing (Appx501-540), arguing that certain prior art "teaches away" from the claimed cells (Appx518, Appx521), and alleging secondary considerations of non-obviousness under virtually every theory recognized by the courts. Appx540-543. In particular, Jadi Cell argued:

- an entirely new definition for "an isolated cell", which was contrary to its own originally proposed definition adopted by the Board (Appx484-486);
- an entirely new definition for the "placing" and "culturing" steps of the claims that imported embodiments from the specification (Appx481-482, Appx488); and
- based on its new (faulty) claim constructions, that the claimed cell is different from the prior art because the claimed process steps are different and, therefore, impart different cell markers (Appx489-493).

Restem replied to Jadi Cell's Response on October 5, 2022. Appx552-594. Restem demonstrated that all of Jadi Cell's arguments were founded upon an incorrect claim construction that disregarded express definitions in the '176 patent and imported embodiments from the specification into the claims. Furthermore, Restem demonstrated, *inter alia*, that each of Majore, Phan, and Kita disclose producing cells according to the same process recited in the claims and, therefore, naturally result in one or more cells having the claimed marker pattern. Appx574-590. Specifically, Restem argued the claimed cells are produced by the two-step

process expressly recited in the claims and do not require additional steps disclosed as embodiments in the specification (Appx568-572), and that Majore, Phan, and Kita each disclose producing a cell by contacting a SL of an umbilical cord with a growth substrate and culturing the SL such that the produced cells are capable of self-renewal and culture expansion. Appx574-578, Appx584-586, Appx587-589. Thus, Restem argued the result of the prior art process–like the claimed process–is to produce one or more cells having the same marker characteristics recited in the claims. Appx577-579, Appx581-582, Appx585-587, Appx588-589.

On November 16, 2022, Jadi Cell filed a Sur-Reply (Appx609-644) that, *inter alia*, falsely asserted, for the first time in the trial, that it provided data comparing Majore's cells to the claimed cells in a Rule 1.132 declaration provided during prosecution of the '176 patent. Appx620. In reality, the Rule 1.132 declaration compared the cells produced according to the claims with cells produced by a protocol that was completely unrelated (and qualitatively different) than Majore. Appx216-217, 11-12, Appx1722-1724, ¶¶62-65, Appx3418-3423, Appx3424-3425.

3. The Board Enters a Final Written Decision

The Board issued its FWD on April 18, 2023. Notably, the Board generally sided with Restem with respect to resolving the parties' disputes over the proper construction of the two disputed claim terms, and agreed with Restem that each of

Majore, Phan, and Kita, produce cells according to the claimed process. For example, the Board:

- Rejected Jadi Cell's argument that the step of "placing a sub-epithelial layer . . . in direct contact with a growth substrate" required placing the SL "interior side down" and "removing Wharton's jelly." Appx20-24.

- Generally adopted Restem's interpretation of "placing a sub-epithelial layer . . . in direct contact with a growth substrate" as meaning "orienting umbilical cord tissue comprising the subepithelial layer such that the subepithelial layer touches a growth substrate to permit culturing." Appx24.

- Agreed with Restem that Majore discloses a cell produced by the process recited in the claims (Appx31-34) and that Majore discloses the "expressed" markers (Appx37-38).

- Agreed with Restem that Phan discloses a cell produced by the process recited in the claims (Appx58-59);

- Agreed with Restem that Kita discloses a cell produced by the process recited in the claims (Appx67-68) and that Kita discloses the "expressed" markers (Appx68-69);

Despite the fact that the Board (1) agreed with Restem in its claim construction, (2) agreed that the prior art produced a cell according to the same process recited in the product-by-process claims, and (3) agreed (for Majore and Kita) that the "expressed" markers are disclosed, the Board inexplicably determined that that the prior art does not anticipate or render obvious the claims because the cells produced by the prior art process do not necessarily meet the recited marker patterns.

Restem timely appealed the Board's FWD. Appx104-108.

On August 29, 2023, an amicus brief was filed *pro se* by the president/CEO of Therapeutic Solutions International, Inc. (TSOI), the alleged exclusive licensee of the '176 patent, wherein the amicus accused two of Jadi Cell's declarants, Dr. Amit Patel (the inventor of the '176 patent and owner of Jadi Cell) and Dr. Camillo Ricordi, of lying under oath during their depositions. Dixon Amicus Brief, Dkt. No. 15. The amicus brief largely repeats the accusations set forth in TSOI's October 24, 2022 Form 8-K filing (*Id*. at 2) with the SEC, which was made after the close of discovery, but before filing of this appeal. The declarations of Drs. Patel and Ricordi were directed to secondary considerations of obviousness, which the Board did not use. Thus, the amicus brief sheds no light on the substantive issues of the current appeal.

SUMMARY OF THE ARGUMENT

The Board's Implicit Claim Construction

The Board's first legal error was an improper claim construction, wherein it "read-in" limitations to the claimed process steps to distinguish the Challenged Claims from the prior art. The Board's improper claim construction was not expressly stated; rather, it was an ***implicit*** claim construction that appeared outside of (and was contrary to) its express claim construction. All claim constructions, whether express or implicit, are reviewed *de novo*. *See Kemin Foods, L.C. v. Pigmentos Vegetales del Centro S.A. de C.V.*, 93 F.App'x 225, 230 (Fed. Cir. 2004)

(reviewing court's implicit claim construction); *Optical Disc Corp. v. Del Mar Avionics*, 208 F.3d 1324, 1334 & n.4 (Fed. Cir. 2000) (same).

The Board provided an eight-page claim construction analysis for the process steps of the Challenged Claims, wherein it determined that the "isolated cell" was produced by the expressly recited, two-step, process without any additional steps. Appx18-24. In so doing, the Board rejected Jadi Cell's attempt to read-in embodiments from the specification, including the additional process steps of orienting the SL "interior down" or isolating the SL from other tissue. Appx18-24. Contrary to its express construction rejecting additional process steps, however, the Board then proceeded to implicitly read-in the "interior down" embodiment and relied on that implicit construction to distinguish the Challenged Claims from the prior art. Specifically, the Board found that the prior art "differs from at least the interior-down embodiment disclosed in the '176 patent, which Patent Owner claims is the focus of the claims at issue." Appx39, Appx61.

Moreover, throughout its analysis, the Board implicitly read-in unspecified "factors" and "conditions" to the process steps, and relied on those additional unspecified implicit constructions as the basis for why an isolated cell produced according to the claimed process would not necessarily produce a cell having the recited markers. The Board also adopted a new implicit construction for the term "an isolated cell" that is directly at odds with the lexicography in the specification, and

inconsistent with the construction that Jadi Cell proposed and the Board adopted at Institution reflecting the express definitions in the specification.

Thus, the implicit claim constructions applied by the Board improperly read-in embodiments from the specification, as well as additional unspecified conditions, and disregarded express definitions in the '176 patent. For this reason alone, the Board's FWD should be reversed.

The Board Misapplied the Law of Inherency

The Board's second legal error was that it applied an improper standard for inherency of product-by-process claims. Specifically, the Board stated that Restem was required to provide "evidence that the marker expression profile is *only* dependent on the process used to produce the claimed cells." Appx40, Appx63, Appx70 (emphasis in original). In other words, the Board required Restem to prove, not only that the prior art teaches the same two-step process as the claims, ***but also that the claimed two-step process actually results in the claimed product*** (*i.e.*, the isolated cell with the specified marker characteristics). The Board's additional requirement departs from the well-established law of inherency that "[a] limitation is inherent if it is the 'natural result flowing from' the prior art's explicit disclosure." *Arbutus Biopharma*, 65 F.4th at 662 quoting *Schering,* 339 F.3d at 1379.

Had the Board applied the correct standard for inherency, it would have concluded that the prior art inherently anticipated the Challenged Claims (as

expressly construed by the Board). This is because there was no dispute during the IPR that the recited markers are imparted by the claimed process for producing the cells, and the Board agreed that the prior art teaches an isolated cell produced by that claimed process. Thus, the natural result flowing from the prior art's teaching of the same claimed process is indisputably that the same isolated cell would be produced, including any specified markers. The Board sidestepped this logical conclusion by misapplying the established case law and further requiring that Restem prove the prior art process steps actually produce the product defined by the two process steps recited in the Challenged Claims. For this separate reason the Board's FWD should be reversed.

The Board did not Support Its Findings For Claim 9

In the FWD, the Board made a separate finding that claim 9, which is directed to culturing cells in media "free of animal components," was not obvious over the combination of, *inter alia*, Kita and Majore. The Board made this finding without any analysis and despite Jadi Cell's own expert admitting there was ample motivation to use media free of animal components, it was known at the priority date, and it was taught by the prior art. Thus, the Board's determination as to dependent claim 9 is not supported by substantial evidence and should be reversed.

STANDARD OF REVIEW

This Court "review[s] the Board's claim construction *de novo* and any underlying factual findings for substantial evidence. *See*, *e.g.*, *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 331-33 (2015).

In the IPR, the Board construed the claim terms according to the standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-17 (Fed. Cir. 2005). *See*, *e.g.*, Appx17. As explained in *Phillips*, the words of the claims themselves are paramount and generally given their "ordinary and customary meaning" to a person of ordinary skill in the art at the time of the claimed invention. *See Phillips*, 415 F.3d at 1312-1313 ("It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude.") (internal quotations and citations omitted); *see also Interactive Gift Exp. Inc. v. Compuserve Inc.,* 256 F.3d 1323, 1331 (Fed. Cir. 2001). Indeed, as this Court has repeatedly explained, "the claim-construction inquiry . . . begins and ends in all cases with the actual words of the claim." *See*, *e.g.*, *Homeland Housewares, LLC v. Whirlpool Corp.*, 865 F.3d 1372, 1375 (Fed. Cir. 2017) (quoting *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998)).

Although the claims must also be read in view of the specification (*see*, *e.g.*, *Phillips*, 415 F.3d at 1313-1316), it is well-settled that limitations and embodiments described in the specification must not be read into the claims. *See*, *e.g.*, *Thorner v.*

Sony Computer Ent. Am. LLC, 669 F.3d 1362, 1366 (Fed. Cir. 2012) ("We do not read limitations from the specification into claims; we do not redefine words. Only the patentee can do that."). As this Court has cautioned, "even when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction." *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1372 (Fed. Cir. 2014) (internal quotation marks and citation omitted); *see also Arthrex, Inc. v. Smith & Nephew, Inc*., 935 F.3d 1319, 1330 (Fed. Cir. 2019)(upholding Board's construction declining to read-in a functional limitation because "the claim does not include any functional limitations" and "[n]owhere does the specification mandate" such functional limitations); *Cadence Pharms. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1369 (Fed. Cir. 2015); *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 913 (Fed. Cir. 2004) ("it is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment—into the claims absent a clear indication in the intrinsic record that the patentee intended the claims to be so limited.").

Anticipation is a question of fact, reviewed for substantial evidence (*In re Gleave*, 560 F.3d 1331, 1334–35 (Fed. Cir. 2009)), while "[t]he ultimate judgment of obviousness is a legal determination," *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398,

427 (2007), which is reviewed *de novo*. *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1297 (Fed. Cir. 2015) (*In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000)). Any underlying factual findings are reviewed for substantial evidence. *Id*. The Board's judgment must be reviewed on the grounds and reasoning upon which it actually relied and set forth in its final written decision. *In re Sang-Su Lee*, 277 F.3d 1338, 1342, 1345-46 (Fed. Cir. 2002) ("The [Board] must set forth its findings and the grounds thereof, as supported by the agency record, and explain its application of the law to the found facts."). A failure of the Board to adequately set forth its finding and explain its reasoning is grounds for reversal. *See, e.g., Google Inc. v. Intellectual Ventures II LLC*, No. 2016-1543, 2017 WL 2924132, at *4 (Fed. Cir. July 10, 2017); *In re Nuvasive, Inc.*, 842 F.3d 1376, 1383 (Fed. Cir. 2016*); Pers. Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 993 (Fed. Cir. 2017).

ARGUMENT

A. THE BOARD LEGALLY ERRED BY USING AN IMPLICIT CLAIM CONSTRUCTION THAT IMPORTED EMBODIMENTS OF THE SPECIFICATION AND OTHER UNSPECIFIED REQUIREMENTS INTO THE PRODUCT-BY-PROCESS CLAIMS

The Board legally erred by importing embodiments of the specification into the Challenged Claims. In the FWD, the Board found it was only necessary to interpret the terms "placing a sub-epithelial layer . . . in direct contact with a growth substrate" and "expresses/does not express" to render a judgment. Appx17-18. In

the FWD the Board expressly provided a correct claim construction for "placing a sub-epithelial layer . . . in direct contact with a growth substrate" (Appx18-24), but then disregarded it by reading-in additional claim limitations when comparing the claims to the prior art. *See, e.g.*, Appx39, Appx61. To be clear, the Board effectively used ***two*** interpretations of the claims in the FWD. An ***express*** claim interpretation, in which the Board correctly declined to read-in limitations, that was used when comparing the claimed process steps to the prior art. Appx18-24, Appx31-34, Appx57-59, Appx67-68. And an ***implicit*** claim interpretation, in which the Board incorrectly read-in limitations, used when comparing the claimed cell markers to the prior art. Appx39, Appx61, Appx28, fn18, Appx63-64, Appx70-71, Appx41. The Board's claim constructions are reviewed *de novo* regardless of whether they are implicit or expressly stated. *See Kemin Foods,* 93 F.App'x at 230 (reviewing court's implicit claim construction); *Optical Disc Corp.*, 208 F.3d at 1334 & n.4 (same).

1. In the Express Claim Construction Analysis, the Board Correctly Determined that the Claimed Cells are Produced by the Two-Step Process Recited in the Claims

The Board interpreted the claimed step of "placing a sub-epithelial layer . . . in direct contact with a growth substrate" for the first time in the FWD. Appx18-24. During the trial, there was no dispute that the process steps of the claims are responsible for producing cells with the recited cell markers. *See, e.g.*, Appx489 ("The Process Steps Impart Functional Differences to the Claimed Cells"); Appx490

("[T]he claimed process steps impart an unexpected gene marker expression to the claimed cells."); Appx226 ("[B]ecause Majore's process of isolating cells produces cells necessarily and inevitably comprising the same cells as the '176 claims, all the characteristics of Majore's cells (including marker pattern) are also necessarily and inevitably the same as the cells produced by the '176 claims."); Appx250, Appx258-259, Appx262-263. Rather, the dispute between the parties was only in the construction of those process steps; *i.e.*, whether the claims simply require the expressly-recited, broad two-step process to produce the claimed product, *i.e.*, cells with the recited markers (according to Restem) or whether the claims require additional unrecited steps disclosed as embodiments in the specification to produce such cells (according to Jadi Cell). Specifically, Jadi Cell asserted that the proper construction of the claims requires a process that includes not only the expressly recited process steps, but also the additional two steps of: (1) orienting the subepithelial layer interior side down; and (2) isolating the SL from all other umbilical cord tissue. Appx481, Appx484-486, Appx488.

To resolve the dispute, the Board began by analyzing the phrases around the claim term for context. Appx20. Specifically, the Board looked to the purpose of the "placing" step as being related to the overall goal of "culturing" the subepithelial layer. *Id*. The Board concluded that "[b]ecause the purpose of the recited process is to culture the cells" the term "placing a subepithelial layer of umbilical cord tissue

in direct contact with a growth substrate" means "to intentionally place umbilical cord tissue comprising the subepithelial layer so that it touches a growth substrate to permit cell culture." *Id*. In support of this interpretation, the Board correctly noted that the disclosures of "subepithelial layer" in the specification "do not uniformly require its isolation from the umbilical cord or removing Wharton's jelly prior to the 'placing' step." *Id*. The Board also considered the specific embodiment disclosed in the specification reciting "dissecting the subepithelial layer from the umbilical cord, washing it to remove Wharton's jelly, and placing it interior side down on a substrate, either in whole or in pieces." *Id*. The Board correctly concluded that "this embodiment is narrower than the remainder of the disclosure…which does not require isolation of the subepithelial layer or removal of Wharton's jelly." *Id*. The Board also correctly concluded that the term "placing a subepithelial layer of umbilical cord tissue in direct contact with a growth substrate" can be "interpreted consistently with the intrinsic record to cover multiple embodiments," and that the "Patent Owner has offered no clear disavowal of claim scope or evidence of broader claims in a parent application that would support interpretation of claim 1 to cover a narrower embodiment only." *Id*.

The Board then correctly applied these same principles to the claim term "direct contact" and concluded that "the Specification does not specify the orientation in all embodiments when discussing placing the subepithelial layer on

the culture substrate, and in some instances indicates that culture occurs without interior side down contact." Appx22. Additionally, the Board correctly noted that the "Patent Owner has provided no evidence of claim disavowal that would lead us to conclude that the Challenged Claims are properly drawn to a portion of the Specification and should be interpreted to require an interior side down orientation." *Id*.

Thus, the Board correctly interpreted the claimed step of "'placing a subepithelial layer of umbilical cord tissue in direct contact with a growth substrate' consistent with its plain meaning and generally consistent with Petitioner's arguments as 'orienting umbilical cord tissue comprising the subepithelial layer such that the subepithelial layer touches a growth substrate to permit culturing.'" Appx24.

2. In Analyzing the Claimed Process Steps, the Board Correctly Determined That Each of Majore, Phan, and Kita Teach an Isolated Cell Produced by the Claimed Two-Step Process as Expressly Construed by the Board

Based on its express construction of the claimed process steps, the Board then performed an analysis to determine whether the prior art disclosed a cell produced by the claimed process steps, as expressly construed by the Board. Appx31-34, Appx57-59, Appx67-68. The Board concluded that each of Majore, Phan, and Kita disclose a cell produced by the same two-step process recited in the claims. *Id*. Regarding Majore, the Board concluded for the first process step (claim element Pre[A]):

> [W]e do not construe "placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate" to require placing the subepithelial layer interior side down in direct contact with the growth substrate. Both Majore and the '176 patent disclose umbilical cord tissue cut into sections and placed into environments fostering cell culture and replication. Ex. 1011, 18; Ex. 1001, 13:57–14:5. Both methods result in adherent cells growing on a plastic growth surface awash in culture media. Ex. 1011, 18; Ex. 1001, 13:57–14:5. Thus, we find Petitioner has established by a preponderance of evidence that Majore teaches limitation [A].

Appx32-33.

The Board also concluded for the second process step (claim element [B]):

> Because Majore discloses cells isolated from an umbilical cord that are proliferative, we find Petitioner has established by a preponderance of evidence that Majore teaches limitation [B].

Appx33-34.

Regarding Phan and Kita, the Board concluded that

> [W]e do not construe "placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate" to require placing the subepithelial layer interior side down in direct contact with the substrate. Both [Phan/Kita] and the '176 patent disclose using explant methods to foster cell culture and replication from tissue harvested from umbilical cord. See Ex. 1017 ¶¶ 1, 41, 42, 45, 88; Ex. 1001, 13:57–14:5. Both methods result in adherent subepithelial cells growing on a plastic growth surface awash in culture media. *Id*. Thus, we find Petitioner has established by a preponderance of evidence that [Phan/Kita] teaches the preamble and limitations [A] and [B].

Appx59, Appx68.

Thus, the Board correctly found that each of Majore, Phan, and Kita produce a cell according to the same two-step process recited in the Challenged Claims under the Board's express constructions.

3. In Analyzing The Claimed Markers, However, The Board Applied an Implicit Claim Construction of the "*Placing*" Step That Improperly Read-In Embodiments From The Specification and Other Unclaimed Requirements

Despite the Board expressly construing the claims as only requiring the two expressly-recited process steps, and finding that Majore, Phan, and Kita each disclose producing cells according to that claimed process, the Board inexplicably concluded that the prior art did not disclose the claimed product—a cell with the specified marker pattern—because the prior art did not teach additional process steps and other requirements believed by the Board to be required to achieve the marker pattern. *See, e.g.*, Appx39, Appx61 (reading in embodiments), Appx28, fn18, Appx63-64, Appx70-71, Appx41 (reading in "factors" and "conditions"). Thus, the Board implicitly construed the claims as requiring additional, unclaimed process steps and requirements, beyond the two steps expressly recited in the claims. In so doing, the Board improperly imported limitations from specific embodiments in the specification (Appx39, Appx61), and also read other vague, unspecified step(s) into the claims ***that are not even described in the specification*** (Appx28, fn18, Appx63-64, Appx70-71, Appx41). Critically, the Board's reasons for finding that the cells

produced by each of the prior art references do not have the claimed markers are based solely upon these erroneous implicit constructions.

(a) The Board's improper reading-in of embodiments from the Specification

Regarding the Majore reference, the Board agreed that "in light of our claim interpretations, we find that Majore discloses a method of producing an isolated cell by placing mammalian umbilical cord tissue in direct contact with a growth substrate and culturing those cells to create a stable cell line capable of self-renewal and culture expansion." Appx39. Nevertheless, the Board held that Majore's cells do not necessarily have the same markers because "Majore's process ***differs from at least the interior-down embodiment disclosed in the '176 patent, which Patent Owner claims is the focus of the claims at issue***." Appx39 (emphasis added). The Board did so, despite concluding as part of its thorough claim construction analysis that the claimed process of producing the isolated cell ***does not require additional steps*** of placing the SL interior side down. Appx22-24. Thus, in comparing the markers of the Challenged Claims to the prior art, the Board relied on an implicit claim construction that imported the "interior-down" embodiment from the specification (*i.e.*, the very embodiment Patent Owner attempted to inject into the claims and the Board rejected in its express claim construction). Significantly, this additional step injected through the Board's implicit construction was the basis for

the Board's conclusion that Majore's process would not have necessarily produced the same markers as recited the Challenged Claims. Appx39.

Similarly, in analyzing Phan, the Board agreed that "[i]n light of our claim interpretations explained above, we find that Phan discloses a method of producing an isolated cell by placing mammalian umbilical cord tissue in direct contact with a growth substrate and culturing those cells to create a stable cell line capable of self-renewal and culture expansion." Appx61. But then the Board held that Phan's cells do not necessarily have the same markers recited in the Challenged Claims because "Phan's process ***differs from at least the interior-down embodiment disclosed in the '176 patent***, which Patent Owner claims is the focus of the claims at issue." Appx61. Once again, the Board made this finding despite concluding as part of its express constructions that the process of producing the isolated cell of the Challenged Claims does not require the additional step of placing the SL interior side down. Appx22-24.

The Board did not provide a full analysis of the third primary reference, Kita, but instead stated that "[o]ur reasoning mirrors our analysis for Grounds 3 and 5." Appx70. Ground 3 asserts obviousness using Majore as the primary reference and Ground 5 asserts obviousness using Phan as the primary reference, in which the Board distinguished the prior art from the Challenged claims because of the implicit

construction requiring that the claimed process include the steps described in the "interior down" embodiment.

A chart showing the express claim construction (in which the Board correctly declined to read-in limitations) contrasted with the implicit claim construction used in the marker analysis (in which the Board read-in embodiments) is provided below:

Express Claim Construction	**Implicit Claim Construction Actually Used In Marker Analysis**
"Because the Specification does not disclose only embodiments in which the subepithelial layer alone is isolated before culturing, or expressly require that the ***interior side down*** of the subepithelial layer is placed onto the culture medium, ***we decline to import those limitations into the claims***." Appx24 (emphasis added). "the Specification ***does not specify the orientation in all embodiments*** when discussing placing the subepithelial layer on the culture substrate, and in some instances indicates that ***culture occurs without interior side down*** contact." Appx22 (emphasis added). "placing a subepithelial layer of umbilical cord tissue in direct contact with a growth substrate" means "***orienting umbilical cord tissue comprising the subepithelial layer such that the subepithelial layer touches a growth substrate to permit culturing***." Appx24 (emphasis added).	Holding Majore does not necessarily produce the claimed markers because "Majore's process ***differs from at least the interior-down embodiment disclosed in the '176 patent, which Patent Owner claims is the focus of the claims at issue***." Appx39 (emphasis added). Holding Phan does not necessarily produce the claimed markers because "Phan's process ***differs from at least the interior-down embodiment disclosed in the '176 patent***, which Patent Owner claims is the focus of the claims at issue." Appx61.

All claim constructions, whether express or implicit, are reviewed *de novo*. *See Kemin Foods,* 93 F.App'x at 230 (reviewing court's implicit claim construction); *Optical Disc Corp.*, 208 F.3d at 1334 & n.4 (same). Absent some clear intent from the intrinsic record to the contrary, it is improper for the Board to import embodiments from the specification into the process steps of the claims. Thus, the Board's implicit constructions are erroneous and should be reversed. *In re Rambus Inc.*, 694 F.3d 42, 47 (Fed. Cir. 2012); *King Pharmaceuticals, Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010); *In re Omeprazole Patent Litigation*, 483 F.3d 1364, 1372 (Fed. Cir. 2007).

(b) The Board's reading-in of unspecified additional limitations to the claims

In addition to reading specific embodiments from the Specification into the claims, the Board's implicit constructions read additional *unspecified* limitations into the claims that are not described anywhere in the patent.

Throughout the FWD the Board held that the prior art does not necessarily produce a cell having the claimed markers (despite the process steps being the same) because marker expression generally can be influenced by various "conditions" and "factors." *See, e.g.*, Appx28, fn18, ("both experts agree that expression and non-expression can be influenced by factors such as culture conditions and cell-to-cell interactions …. the '176 patent does not mention any factor that could change marker expression, such as the media or culture conditions, and does not describe or claim

unique tissue culture conditions or media to achieve any desired result"); Appx53, ("the evidence of record, including Dr. Olson's own testimony, shows that multiple conditions can affect marker expression."); Appx64, ("multiple conditions can affect marker expression."); Appx71, ("multiple conditions can affect marker expression."); Appx41, ("multiple factors can influence marker expression… factors such as time, temperature, and cell source"); Appx41, ("multiple factors can influence marker expression"); Appx63, ("the evidence of record shows that multiple factors can influence the marker expression profile"); Appx70, ("the evidence of record shows that multiple factors can influence the marker expression profile.")

There is no dispute that various conditions and factors can alter marker expression generally, but this misses the point. The '176 patent does not disclose that any conditions or factors (other than deriving cells from the SL) are required to obtain cells with the recited markers according to the claimed process. To the contrary, the '176 patent makes abundantly clear that ***any of a variety of techniques and conditions can be used to obtain the claimed cells***. The '176 patent explains that the SL "can be cultured in any media capable of producing explants therefrom" (Appx94, 2:21-22) using "any substrate capable of deriving explants" (Appx94, 2:29-30), and using "various culturing conditions" (Appx94, 2:4-42), including *e.g.*, normoxic/hypoxic conditions (Appx94, 2:45-47; Appx98, 9:65-10:2), with/without

use of enzymes (Appx94, 2:47-52), culturing for any period of time sufficient to produce primary cultures (Appx98, 9:16-18), with or without animal components (Appx97, 7:25-28), and employing one or more of various growth factors (Appx98, 10:7-12). Indeed, the Board acknowledged that, "[a]ccording to the '176 patent, the target allogenic cell or stem cell population is obtained from the subepithelial layer (SL) of a mammalian umbilical cord using one of a 'variety of techniques' so long as the technique 'allows such extraction without significant damage to the cells.'" Appx4, quoting Appx97, 8:1-2, 8:34-38. The Board also acknowledged that the '176 patent provides no guidance for how any additional "factors are to be controlled to ensure that the claimed marker expression results." Appx42.

Consistent with the '176 patent's broad disclosure, in the expressly stated claim construction analysis, the Board looked to the specification for the conditions required to produce the claimed cells and (correctly) determined that the broad two-step process, without any other conditions or steps, was the proper construction for the process used to produce a cell having the recited markers. Appx18-24.

Thus, the Board's repeated reference to unspecified "conditions" and "factors" (as variables to marker expression) to conclude that the prior art process does not result in the claimed cells is an implicit claim construction that improperly injects additional ***unknown*** limitations into the claims. This implicit construction is not only wholly unsupported and ambiguous, but also contrary to the specification which

makes clear that any of a variety of techniques and conditions can be used to obtain the claimed cell. Thus, the Board's implicit construction should be reversed. *Wi-Fi One, LLC v. Broadcom Corporation*, 887 F. 3d 1329, 1346 (Fed. Cir. 2018) (rejecting patentee's proposed narrow construction in an IPR to avoid a finding of anticipation, the court noted that while the patentee's proposed construction appeared reasonable from just looking at the words of the claim, when the specification was considered, it was evident that the patentee's proposed construction was unreasonable.); *Erbe Elektromedizin GmbH v. International Trade Com'n*, 566 F.3d 1028, 1034–37 (Fed. Cir. 2009) ("We generally do not construe claim language to be inconsistent with the clear language of the specification; usually, it is dispositive." (internal quotations omitted)). Moreover, it is improper to read-in structures used in the act of performing process steps. *See, Schumer v. Laboratory Computer Systems, Inc.*, 308 F.3d 1304, 1312, (Fed. Cir. 2002) ("[A] method claim which is not tied to a particular device but that operates to change articles or materials to a different state or thing … must be interpreted to cover any process that performs the method steps.").

The Board's reading-in of unspecified process steps to the claims is also evident in its reliance on the Rule 1.132 Declaration submitted during prosecution of the '176 patent. Specifically, the Board stated that it found persuasive the evidence presented in the underlying prosecution of the '176 patent showing that differences

in the method of obtaining cells from umbilical cord tissue could change the marker profile of cells produced. Appx42-43.[4] Indeed, the Board concluded that such evidence shows "that use of a ***different process*** to create an isolated cell can result in a different marker expression profile." Appx43 (emphasis added). The Board made this finding despite that fact that it concluded the prior art teaches a cell produced by the ***same process*** of the claim. *Supra* §A.2; Appx31-34, Appx57-59, Appx67-68. The fact that the Board found evidence of ***differences in the method*** compelling confirms that the Board read-in additional (unspecified) steps into the claimed process that would purportedly make the claimed cells different from the prior art. Reading-in of any additional steps (specified or unspecified) not recited in the claim is improper. *In re Rambus*, 694 F.3d at 47; *King Pharmaceuticals,* 616 F.3d at 1275; *In re Omeprazole*, 483 F.3d at 1372.

Additionally, the Board's implicit constructions disregard the ***product-by-process nature of the claim***. Indeed, the product-by-process claims themselves recite that the two step method produces cells having the enumerated marker pattern. *See* Appx103, claim 1. Thus, because the Board agreed that the prior art teaches

[4] The Rule 1.132 declaration provided data comparing gene expression of cells obtained via explant procedure (*i.e.*, the type of procedure used by the '176 patent, Majore, Phan, and Kita) with gene expression of control cells obtained from an entirely different process of enzymatically digesting umbilical cord tissue. Appx216-217, 11-12; Appx1722-1724, ¶¶62-65. Moreover, the gene expression data presented in the Rule 1.132 declaration did not test for the markers recited in claim 1. Appx3418-3423, Appx3424-3425.

producing cells according to the claimed process, but then concludes the prior art cells are not necessarily the same, the Board must be imputing some difference not expressly recited in the claimed process that changes the outcome (*i.e.*, the markers produced). This implicit inclusion of additional, unspecified requirement(s) to obtain cells having the recited markers is apparent in the Board's statement that "[t]he '176 patent Specification also does not address whether every disclosed embodiment or the broad process parameters disclosed therein would necessarily result in an isolated cell with a marker profile consistent with claim 1." Appx39-40 (Majore), Appx62 (Phan). This statement is irreconcilable with the Board's express determination (correctly) that the claimed cell ***is produced*** by the broader two-step process recited in the claims, and does not require additional process steps disclosed as embodiments of the specification. Appx18-24.

The Board's express determination that the broader two-step process recited in the claims is sufficient to produce cells having the recited markers is amply supported by the '176 patent specification, which unambiguously teaches that the key to obtaining cells with the claimed marker pattern is in only deriving the cells from the SL. Appx94, 1:33-41, Appx97, 7:67-8:6, Appx97, 8:3-6. Indeed, the specification makes clear, throughout, that various processes/conditions/treatments can be used to obtain the claimed cells. Appx94, 2:21-22, Appx94, 2:29-30, Appx94, 2:4-42, Appx94, 2:45-47, Appx98, 9:65-10:2, Appx94, 2:47-52, Appx98, 9:16-18,

Appx97, 7:25-28, Appx98, 10:7-12. And the Board acknowledged that the '176 Specification does not provide any guidance on any other culture condition that would be required to obtain the claimed cells. Appx42. Thus, the Board's implicit construction of the claimed process as requiring additional unspecified steps not recited in the claims, or even described in the specification, to produce cells with the claimed markers was plainly improper.

4. The Board's Implicit Reading-In of Process Steps Vitiates the Function of the Product-By-Process Claims

The Board's implicit claim construction results in a product-by-process claim that ***recites a process that does not necessarily produce the claimed product***. Because the Board agreed that the process of Majore, Phan, and Kita is the ***same*** as the claimed process, as expressly construed by the Board, but does not necessarily produce the recited markers, the Board has implicitly determined that the ***claimed process*** does not necessarily produce an isolated cell having the claimed markers. This result vitiates the core principle of product-by-process claims.

It is axiomatic that a product-by-process claim defines a product by reciting the process of making the product in the claim. *Mentor Corp. v. Coloplast, Inc.*, 998 F.2d 992, 997 (Fed. Cir. 1993), reh'g denied, in banc suggestion declined, (Nov. 1, 1993) ("product-by-process claims recite how a product is made"). Indeed, product-by-process claim are employed when a product cannot otherwise be defined except by setting forth the process of its manufacture. *Greenliant Systems, Inc. v. Xicor LLC*,

692 F.3d 1261, 1268 (Fed. Cir. 2012) ("'Product-by-process claims … enable an applicant to claim an otherwise patentable product that resists definition by other than the process by which it is made,'" citing *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985).).

Here, the patentee, by electing to use the product-by-process format, acknowledges that the claims cannot be adequately defined based on marker pattern alone and, therefore, must be (and were) defined by the process of making the cells.[5] Despite this, the Board has implicitly divorced the recited process from the produced product, and determined that the claimed process does not necessarily produce the isolated cells having the recited marker pattern. The Board did so without providing any analysis of or citing any support in the intrinsic evidence. Critically, as discussed above, the '176 patent specification makes clear that the recited markers are simply characteristics of the cells produced by the recited process steps. *See, e.g.*, '176, 7:65-67 ("Isolated cells from the SL can have a variety of characteristic markers that distinguish them from cell [sic] previously isolated from umbilical cord samples."); *id* at 8:3-6 ("Various cellular markers that are either present or absent

[5] Indeed, the marker pattern recited in claim 1 is not a single pattern, but covers ***over 80,000 possible patterns*** achieved from all the permutations of selecting three "expressed" markers and five "non-expressed" markers from the respective lists. This is compounded by the fact that the "explant" methods recited in the '176 patent would produce a heterogeneous population of cells. Appx1712-1714, Appx1716-1718.

can be utilized in the identification of the SL-derived cells, and as such, can be used to show the novelty of the isolated cells.") In fact, the '176 patent makes clear that the key to obtaining cells having the recited markers is to ***simply derive them from SL tissue*** of umbilical cord. Appx94, 1:33-41; Appx97, 7:67-8:6.

Likewise, the product-by-process claims themselves make clear that the expressly-recited two step method produces an isolated cell having the enumerated marker pattern. *See* Appx103, claim 1. Thus, the Board's unsupported conclusion that the processes taught by Majore, Phan, and Kita do not result in isolated cells having the same marker patter as the claims disregards the fundamental nature of product-by-process claims by improperly importing additional steps into the claimed process. This is clear legal error.

5. The Board's Implicit Reading-In of Additional Limitations Defeats the Notice Function of The Claims

The Board's implicit constructions also eviscerate the notice function of patent claims.

Jadi Cell was free to choose how to claim its invention, and it chose to define the isolated cell by the process used to obtain it. *Abbott Lab'ys v. Sandoz, Inc.*, 566 F.3d 1282, 1294 (Fed. Cir. 2009) ("the inventor is absolutely free to use process steps to define this product. . . . Because the inventor chose to claim the product in terms of its process, however, that definition also governs the enforcement of the bounds of the patent right."). Importantly, the claims provide notice to the public of

the scope of protection of the invention. *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006) ("The purpose of a patent claim is to define the precise scope of a claimed invention, thereby giving notice both to the examiner at the U.S. Patent and Trademark Office during prosecution, and to the public at large, including potential competitors, after the patent has issued." (internal quotations omitted)); *see also Phillips*, 415 F.3d at 1319 (warning of risks of changing "the meaning of claims in derogation of the indisputable public records consisting of the claims, the specification and the prosecution history, thereby undermining the public notice function of patents." (internal quotations omitted); *PSC Computer Prod., Inc. v. Foxconn Int'l, Inc.*, 355 F.3d 1353, 1359–60 (Fed. Cir. 2004) ("[O]ne of ordinary skill in the art should be able to read a patent, to discern which matter is disclosed and discussed in the written description, and to recognize which matter has been claimed. . . . The ability to discern both what has been disclosed and what has been claimed is the essence of public notice. It tells the public which products or processes would infringe the patent and which would not.)

Reading-in unrecited process limitations from embodiments (*supra* §A.3.(a)) or unspecified "factors" and "conditions" that, according to the Board, ***may or may not*** be responsible for the markers (*supra* §A.3.(b)) would render the scope of the patent ambiguous leaving the public to guess about what steps would need to be practiced in order to infringe the claims. *Abbott Lab'ys,* 566 F.3d at 1293 ("[P]rocess

terms in product-by-process claims serve as limitations in determining infringement." (internal quotations omitted)). Thus, Board's implicit constructions completely undermine the notice function of the claims.

6. The Board's Implicit Reading-In of Additional Limitations Was a New Construction That Constituted a New Ground of Rejection

The Board's implicit construction of unspecified "factors" and "conditions" as being required by the process steps to produce the claimed cells (*supra* §A.3.b.) was an entirely new construction that neither party proposed. Indeed, the requirement of unspecified "factors" and "conditions" in the process steps was stated by the Board for the first time in the FWD. *Supra* §A.3.b. It is well settled that, when the Patent Office alters its claim constructions "midstream," the law requires that the Board "must give reasonable notice of the change" and "the opportunity to present argument under the new theory." *SASInst., Inc. v. ComplementSoft, LLC.*, 825 F.3d 1341, 1351 (Fed. Cir. 2016), rev'd and remanded sub nom. *SASInst., Inc. v. Iancu*, 138 S. Ct. 1348, 200 L. Ed. 2d 695 (2018); *see also TQ Delta, LLC v. Dish Network LLC*, No. 2018-1799 (Fed. Cir. 2019); *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1080 (Fed. Cir. 2015). Here, Restem was deprived of the opportunity to present arguments under the Board's implicit claim construction. Thus, for this additional reason, the FWD should be reversed.

B. THE BOARD LEGALLY ERRED BY DISREGARDING EXPRESS DEFINITIONS IN THE '176 PATENT

The Board further distinguished the claims from the prior art by applying an incorrect interpretation of "an isolated cell" that contradicts its own preliminary interpretation and, more importantly, the express definitions in the '176 patent. While the Board declined to expressly construe the term "an isolated cell" in the FWD (Appx17-18), the Board's interpretation of "express/does not express" implicitly includes a construction of "an isolated cell" that ignores the express definitions of the '176 patent.

In the Institution Decision, the Board provided a provisional interpretation for the term "an isolated cell" recited in the challenged claims. Appx382-383. Specifically, the Board interpreted "an isolated cell" in a manner that was generally consistent with Jadi Cell's originally proposed definition as meaning "***one or more cells*** isolated from the subepithelial layer of a mammalian umbilical cord." Appx383 (emphasis added). The Board adopted this interpretation based on the express definitions of the '176 patent, which defines "a cell" to be "one or more of such cells" and defines "isolated cell" as "a cell that has been isolated from the subepithelial layer of a mammalian umbilical cord." Appx383 citing Appx96, 6:29-30, 6:32-34. The Board correctly recognized that these definitions should be read together to arrive at its definition, and recognized its interpretation to be consistent with the Federal Circuit's construction of "a" or "an". *Id*. citing *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (Fed. Cir. 2000).

In the Patent Owner Response, however, Jadi Cell urged the Board to abandon its original definition (argued for by Jadi Cell) and instead interpret "an isolated cell" to mean a plurality or a population of cells. Appx484-486. Restem argued the Board should maintain its original interpretation as mandated by the intrinsic evidence and law on claim construction. Appx567-568.

In the FWD, the Board declined to expressly construe the term an "isolated cell," but instead adopted a new interpretation of this term within its analysis of the terms "expresses"/"does not express". Appx17-18. Specifically, the Board stated that "consistent with our interpretation of 'isolated cell' as indicating ***a cell population*** and generally consistent with Petitioner's proposed interpretation, we interpret 'expresses' to mean that 'the marker is confirmed present relative to a control sample,' and that 'does not express' means that 'the marker is confirmed absent relative to a control sample.'" Appx28 (emphasis added).

The Board provided no analysis or explanation whatsoever for why it disregarded its own preliminary definition of "isolated cell" and no analysis or explanation for why it disregarded the express definitions of the '176 patent. Rather, the Board simply looked to extrinsic evidence of how "marker analysis" was performed at the time of the alleged invention (Appx26-28), and summarily concluded that "isolated cell" means a cell "population." Appx28. Based on this interpretation, the Board stated that "evidence of expression or non-expression

patterns as recited in the Challenged Claims can be used to identify and distinguish the isolated ***cell population*** from other ***cell populations***." Appx28. Thus, throughout the FWD, the Board incorrectly analyzed the prior art looking for "populations" of cells having specified markers, when the claims, as properly construed, merely require "one or more" cells having the specified markers.[6]

Even if the Board is correct that marker expression was ordinarily analyzed in terms of "populations" of cells at the priority date, "a definition of a claim term in the specification will prevail over a term's ordinary meaning if the patentee has acted as his own lexicographer and clearly set forth a different definition." *3M Innovative Properties Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1371 (Fed. Cir. 2003); *see also Jack Guttman, Inc. v. Kopykake Enterprises, Inc.*, 302 F.3d 1352, 1360–61 (Fed. Cir. 2002) ("Where, as here, the patentee has clearly defined a claim term, that definition usually is dispositive; it is the single best guide to the meaning of a disputed term.")

Here, Jadi Cell clearly acted as its own lexicographer by providing express definitions for the meaning of "an isolated cell." Appx96, 6:29-34. Indeed, the Board

[6] Moreover, what constitutes a "population" of cells is not at all clear. The Board did not explain how many cells, or what percentage of cells, must express a marker to be a "population" of such cells, and the '176 patent provides no guidance on what the Board's "population" might mean. Thus, it is impossible to make any comparisons between the claims and the prior art based on the Board's implicit construction.

even acknowledged in the Institution Decision that the '176 patent provides such an express definition, ***and adopted Jadi Cell's proposed construction which reflected that definition***. Appx383. Thus, that definition must prevail even if cell markers were typically analyzed in terms of populations of cells. Accordingly, the Board erred by disregarding the specification's express definitions without any analysis or explanation.

C. THE BOARD MISSAPPLIED THE LAW OF INHERENCY TO THE PRODUCT-BY-PROCES CLAIMS

This appeal is at the intersection of the law on inherency and the law on product-by-process claims. While the Board correctly found that the prior art teaches a cell produced by the same process steps as recited in the Challenged Claims, the Board erred by holding that, to prove inherency Restem was further required to provide "evidence that the marker expression profile is *only* dependent on the process used to produce the claimed cells." Appx40, Appx63, Appx70 (emphasis in original). In other words, the Board required Restem to prove, not only that the prior art teaches the same process recited in the claims (which necessarily leads to the same result), but also that the ***claimed process actually produces the claimed cells with the specified marker patterns***. There is no such requirement.

"A limitation is inherent if it is the 'natural result flowing from' the prior art's explicit disclosure." *Arbutus Biopharma*, 65 F.4th at 662 quoting *Schering,* 339 F.3d at 1379. "A patent can be invalid based on inherency when the patent itself makes

clear that a limitation is not an additional requirement imposed by the claims ... but rather a property necessarily present." *Id*. citing *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020). "Inherent anticipation requires 'merely that the disclosure of the prior art is sufficient to show that the ***natural result flowing from the operation as taught in the prior art would result in the claimed product.***'" *Id*. (emphasis added) quoting *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343–44 (Fed. Cir. 2005). "Insufficient prior understanding of the inherent properties of a known composition does not defeat a finding of anticipation." *Id*. quoting *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1349 (Fed. Cir. 1999).

Here, the law on inherency must be applied to product-by-process claims. Product-by-process claims are the exception to the "general rule requiring claims to define products in terms of structural characteristics." *Atl. Thermoplastics Co. v. Faytex Corp.*, 970 F.2d 834, 845 (Fed. Cir. 1992). In evaluating patentability of a product-by-process claim, the focus generally is on the product. *Amgen Inc. v. F. Hoffman–La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009); *In re Thorpe*, 777 F.2d at 697; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006).

The process recited in a product-by-process claim is not irrelevant, however, when the process imparts structural features to the claims. *Greenliant Sys.,* 692 F.3d at 1268 ("Patent Office in determining patentability considers the process in which

a product is formed if that process imparts distinctive structural characteristics."); *Kamstrup A/S v. Axioma Metering UAB*, 43 F.4th 1374, 1381 (Fed. Cir. 2022) ("[I]f the process by which a product is made imparts 'structural and functional differences' distinguishing the claimed product from the prior art, then those differences 'are relevant as evidence of no anticipation' although they 'are not explicitly part of the claim.'" (quoting *Amgen,* 580 F.3d at 1365–67); *SmithKline*, 439 F.3d at 1319 ("If those product-by-process claims produced a different product than that disclosed by the [prior art], there would be an argument that the [prior art] did not anticipate."); *In re Garnero*, 56 CCPA 1289, 412 F.2d 276, 279 (1969) (finding that certain process limits are "capable of construction as structural ... limitations"); Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010) ("The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.) Indeed, it is well established that the process of a product-by-process claim should be considered for patentability when that process imparts distinctive structural characteristics. *Greenliant*, 692 F.3d at 1268.

In the FWD, the Board did not provide any analysis or make any findings as to whether the claimed process *actually* imparts the specified markers. This is not

surprising because during the IPR trial, there was ***no dispute*** that the process recited in the challenged product-by-process claims was responsible for imparting the recited markers. *See, e.g.*, Appx489 ("The Process Steps Impart Functional Differences to the Claimed Cells"); Appx490 ("[T]he claimed process steps impart an unexpected gene marker expression to the claimed cells."); Appx226 ("[B]ecause Majore's process of isolating cells produces cells necessarily and inevitably comprising the same cells as the '176 claims, all the characteristics of Majore's cells (including marker pattern) are also necessarily and inevitably the same as the cells produced by the '176 claims."); Appx250, Appx258-259, Appx262-263.[7]

Even if the Board had deemed it necessary to independently determine whether the recited process steps actually impart the markers, this would have necessarily involved consideration of the '176 patent specification. *See Kamstrup A/S*, 43 F.4th at 1381–82 (holding the district court correctly considered, *inter alia*,

[7] To the extent Jadi Cell now asserts that the markers are imparted by the process according to its construction, but disputes that the markers are imparted by the process according to the construction ultimately adopted by the Board, the ***burden was on Jadi Cell*** to provide evidence that the claimed markers are not imparted by the claimed process steps. *See 3M Innovative Properties,* 350 F.3d at 1371 (Fed. Cir. 2003) ("[E]ven words of limitation that can connote with equal force a structural characteristic of the product or a process of manufacture are commonly and by default interpreted in their structural sense, unless ***the patentee has demonstrated otherwise***." (emphasis added)); *see also In re Nordt Dev. Co.*, LLC, 881 F.3d 1371, 1375-76 (Fed. Cir. 2018). Jadi Cell provided no such evidence. Moreover, Jadi Cell is bound by the arguments it made before the Board. *Greenliant Sys.,* 692 F.3d at 1271 ("Nor does it matter here whether [a particular feature] actually imparted the cited structural differences because Xicor argued that it did.")

the intrinsic evidence, including the patent specification, to determine if distinct structural characteristic were imparted); *Purdue Pharma L.P. v. Epic Pharma*, LLC, 811 F.3d 1345, 1353-54 (Fed. Cir. 2016).

Here, the '176 patent specification makes clear that the recited markers are simply characteristics of the cells produced by the process steps. *See, e.g.*, Appx97, 7:65-67 ("Isolated cells from the SL can have a variety of characteristic markers that distinguish them from cell [sic] previously isolated from umbilical cord samples."); Appx97, 8:3-6 ("Various cellular markers that are either present or absent can be utilized in the identification of the SL-derived cells, and as such, can be used to show the novelty of the isolated cells.") In fact, the '176 patent makes clear that the key to obtaining cells having the recited markers is to ***simply derive them from SL tissue*** of umbilical cord. Appx94, 1:33-41 ("In one aspect, for example, an isolated cell that is capable of self-renewal and culture expansion and is obtained from a subepithelial layer of a mammalian umbilical cord tissue is provided. Such an isolated cell expresses at least three cell markers selected from CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, or CD105, and does not express at least three cell markers selected from CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR."); Appx97, 7:67-8:6 ("It should be noted that these isolated cells are not derived from the Wharton's Jelly, but rather from the SL"). Thus, the '176 patent itself makes clear that the markers are not an additional

requirement imposed by the claims, but rather a property of the cells produced by the recited process. *See Arbutus Biopharma,* 65 F.4th at 662; *Hospira,* 946 F.3d at 1332.

The '176 patent also makes clear that the method of deriving such cells from the SL is not limited to any one particular method, and various techniques and culturing conditions can be used to obtain the claimed cells, with the only unchanging requirement being that the cells are obtained from the SL tissue. *See supra* §A.3.b, Appx94, 2:21-22, Appx94, 2:29-30, Appx94, 2:4-42, Appx94, 2:45-47; Appx98, 9:65-10:2, Appx94, 2:47-52, Appx98, 9:16-18, Appx97, 7:25-28, Appx98, 10:7-12.

In view of the '176 patent specification, as explained *supra* §A.1, the Board correctly determined that the process steps for producing the cells having the claimed markers are broader than any individual embodiment disclosed in the specification. Appx17-24. The Board also correctly determined that the prior art teaches producing a cell according to the same process steps. *Supra* §A.2.

Contrary to (1) the agreement of the parties that the claimed process steps impart the recited markers, (2) the teachings of the specification showing that the markers are simply characteristics of cells isolated from the SL tissue, and (3) the Board's own claim construction stating that the claimed isolated cell is produced by the expressly stated two-step process, the Board nonetheless concluded that the prior

art cells do not inherently have the same markers. Appx43, Appx63, Appx70. The Board arrived at this result by applying an incorrect standard for inherency. Specifically, the Board stated (for the first time in the FWD) that "Petitioner has not provided any evidence that the marker expression profile is *only* dependent on the process used to produce the claimed cells." Appx40, Appx63, Appx70 (emphasis in original). In so doing, the Board barred Restem from relying on case law showing that process steps are relevant to an inherency analysis when they impart distinctive structural characteristics. Appx40, fn 22.

Evidence sufficient to support a conclusion of inherency does not require that Restem show "the marker expression profile is *only* dependent on the process used to produce the cells" (Appx40, Appx63, Appx70 (emphasis in original)). Rather, the quantum of evidence required to support a conclusion of inherency only requires that Restem show the marker expression profile is the natural result flowing from the prior art's explicit disclosure, particularly given that the '176 patent makes clear (and the parties agreed) that the markers are merely a property of the cells produced by the claimed process. *See Arbutus Biopharma,* 65 F.4th at 662; *Schering,* 339 F.3d at 1379.

Here, it was undisputed that the marker patterns were imparted by the process recited in the challenged claims. The only dispute was the proper construction of those steps: *i.e.*, whether the steps included embodiments of the specification as a

requirement to achieve the cells having the claimed markers (according to Jadi Cell) or whether the expressly recited two-step process produced the cells having the claimed markers (according to Restem). Once the Board construed the process steps as ***not*** requiring any additional steps from the specification, and determined that the prior art teaches the ***same*** process steps of the Challenged Claims, then the natural result of the prior art processes is to produce a cell having the same marker patterns as recited in the Challenged Claims. Indeed, the Board's contrary holding leads to an illogical result for product-by-process claims; *i.e.*, even though the prior art discloses producing a product according to same process recited in a product-by-process claim, it somehow does not anticipate the claimed product. Such a result, if upheld, would encourage claims drafting gamesmanship by patentees while unduly burdening competitors in their search for prior art.

The Board's additional inherency requirement is also contrary to established case law that "[t]o anticipate, the prior art need only meet the inherently disclosed limitation ***to the same extent as the patented invention***." *Arbutus Biopharma,* 65 F.4th at 664bico; *King Pharmaceuticals,* 616 F.3d at 1276 (rejecting the argument that a prior art method did not "necessarily result" in a claimed limitation when the prior art described using the same method as the patent). Here, according to both parties and the '176 specification, the natural result of deriving cells from SL tissue is a cell having the specified markers. Appx489, Appx490, Appx226. Appx250,

Appx258-259, Appx262-263 Appx94, 1:33-41, Appx97, 7:67-8:6, Appx97, 8:3-6. According to the '176 specification and claims (as expressly construed by the Board), the only steps required to produce a cell having the recited markers are simply (1) "placing a [SL] of a mammalian umbilical cord tissue in direct contact with a growth substrate;" and (2) "culturing the [SL] such that the isolated cell from the [SL] is capable of self-renewal and culture expansion." *Supra* §A.1. Thus, to show inherency to the same extent as the patented invention, Restem need only show that the prior art teaches the two-step method of producing an isolated cell according to the claims. *Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 664 (Fed. Cir. 2023). Restem did not need to also show that the markers are "only" dependent on those two steps.

An isolated cell produced by the claimed two-step method is undeniably disclosed in the prior art (Appx31-34, Appx58-59, Appx67-68) and, therefore, the markers of the cells produced by that two-step process are an inherent feature of the prior art. In other words, the markers present on the cells produced by the prior art process is the natural result flowing from the prior art's process. *King Pharmaceuticals,* 616 F.3d at 1276; *see also MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) ("[T]o the extent the embodiment in the patent achieves [the limitation], so does the [prior art].") Accordingly, the

Board's injection of a new requirement into the inherency analysis was legal error and should be reversed.

D. THE BOARD'S DETERMINATION THAT RESTEM DID NOT DEMONSTRATE THAT CLAIM 9 IS OBVIOUS IS UNSUPPORTED

In the FWD, the Board determined that claim 9 of the '176 patent (Ground 8) was not obvious over the combination of, *inter alia*, Kita and Majore for the same reasons as claim 1, and also because "the evidence of record showing a component of bovine serum in the culture media favors Patent Owner." Appx74. The Board's determination is unsupported and must be reversed.

Claim 9 recites:

> 9. The isolated cell of claim 1, wherein culturing comprises culturing in a culture media that is free of animal components.

Restem argued that performing the "culturing" step in a media that is "free of animal components" would be obvious over Kita in view of Majore's disclosure to "avoid[] the use of any xenogenic media supplements" (Appx1932, right col., second para), combined with the fact that use of chemically defined media or human only components was common in the field of MSC biology. Appx273. Jadi Cell's own expert admitted that the media supplement used in Majore's protocol was, in fact, free of animal components (Appx2854, 263:14-264:15), and also acknowledged that there was ample motivation to use media "free of animal components" at the priority date of the '176 patent. Appx2853, 260:7-261:19. Specifically, Jadi Cell's expert

admitted that there was a "long list" of known reasons to avoid animal components at the priority date of the '176 patent, including "safety" and avoiding "regulatory problems." Appx2853, 260:7-261:19.

Despite Jadi Cell's own expert admitting that use of media free of animal components was known at the priority date, was taught by Majore, and that there was ample motivation to use media free of animal components, the Board found without analysis or explanation that "evidence of record showing a component of bovine serum in the culture media favors Patent Owner." Appx74. The Board's determination is clearly unsupported and must be reversed. *In re Sang-Su Lee*, 277 F.3d at 1342, 1345-46 ("The [Board] must set forth its findings and the grounds thereof, as supported by the agency record, and explain its application of the law to the found facts.").

CONCLUSION

For all the foregoing reasons the Board's FWD should be reversed.

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ADDENDUM

Contents of Addendum

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571-272-7822

Paper 42
Date: April 18, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

RESTEM, LLC.,
Petitioner,

v.

JADI CELL, LLC,
Patent Owner.

IPR2021-01535
Patent 9,803,176 B2

Before CHRISTOPHER G. PAULRAJ, ROBERT A. POLLOCK, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)

Denying Petitioner's Motion to Exclude Evidence

Denying Patent Owner's Motion to Exclude Evidence
37 C.F.R. § 42.64

I. INTRODUCTION

We have jurisdiction to conduct this *inter partes* review under 35 U.S.C. § 6, and this Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons that follow, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–15 ("the Challenged Claims") of U.S. Patent No. 9,803,176 B2 (Ex. 1001, "the '176 patent") are unpatentable.

A. Summary of Procedural History

RESTEM, LLC, ("Petitioner") filed a Petition pursuant to 35 U.S.C. §§ 311–319 requesting an *inter partes* review of claims 1–15 of the '176 patent. Paper 1 ("Pet."). Jadi Cell, LLC, ("Patent Owner") filed a Patent Owner Preliminary Response ("Prelim. Resp."). Paper 7. Based on the record then before us, we instituted trial with respect to the Challenged Claims on all grounds. Paper 8, 47 ("Inst. Dec.").

After institution of trial, Patent Owner filed a Response (Paper 15, "PO Resp."), Petitioner filed a Reply to Patent Owner's Response (Paper 22, "Pet. Reply"), and Patent Owner filed a Sur-reply to Petitioner's Reply (Paper 26, "PO Sur-Reply").

Both parties filed motions to exclude evidence and replies in support of those motions (Patent Owner: Papers 29, 37; Petitioner: Papers 30, 36). Both parties opposed each other's motions to exclude (Patent Owner: Paper 33; Petitioner: Paper 32).

We heard oral argument on February 10, 2023. A transcript of that hearing is entered as Paper 41 ("Tr."). Petitioner bears the burden of proving unpatentability of each claim it has challenged by a preponderance of the evidence, and the burden of persuasion never shifts to Patent Owner.

See 35 U.S.C. § 326(e) (2018); 37 C.F.R. § 42.1(d); *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

B. Real Parties in Interest

Petitioner identifies RESTEM LLC as the real party-in-interest for Petitioner. Pet. 1.

Patent Owner identifies Jadi Cell, LLC, as owner and real party-in-interest of the '176 patent. Paper 4, 2.[1]

C. Related Matters

Petitioner states that no related litigation matter is pending and that the "application that matured into the '176 patent was used for a priority claim for pending U.S. Application No. 15/799,743, filed on October 31, 2017, which was used for a priority claim to pending U.S. Application No. 17/322,672, filed on May 17, 2021." Pet. 1.

Patent Owner identifies no related matters. Paper 4, 2.

D. The '176 Patent

The '176 patent, titled "Methods and Compositions for the Clinical Derivation of An Allogenic Cell and Therapeutic Uses" issued October 31, 2017, from Application No. 13/732,204 ("the '204 application), filed August 22, 2013. Ex. 1001, codes (21), (22), (45), (54).

The '176 patent discloses "an allogenic cell or stem cell population that can be used for treating a wide range of conditions" along with methods of "isolating, culturing, developing, or otherwise producing these cells." *Id.*

[1] Paper 4 is not paginated. We cite to Paper 4 as if paginated beginning on the cover page.

at 7:23–30. The definitions of allogenic cells and stem cells are not disputed by the parties. By way of background, however, an "allogenic" cell is one that is "genetically different although belonging to or obtained from the same species." *See* Ex. 3001.[2] "Stem cells" are cells with "the ability to differentiate along different lineages and the ability to self-renew." Ex. 3002,[3] Abstract. "Mesenchymal stem cells (MSCs) are stromal cells that have the ability to self-renew and also exhibit multilineage differentiation. MSCs can be isolated from a variety of tissues, such as umbilical cord, endometrial polyps, menses blood, bone marrow, adipose tissue, etc." *Id.*

According to the '176 patent, the target allogenic cell or stem cell population is obtained from the subepithelial layer (SL) of a mammalian umbilical cord using one of a "variety of techniques" so long as the technique "allows such extraction without significant damage to the cells." Ex. 1001, 8:1–2, 8:34–38. Figure 1 of the '176 patent, reproduced below, shows a cross section of an umbilical cord.

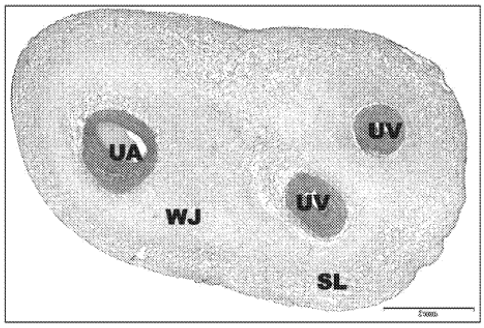

FIG. 1

[2] American Heritage Dictionary of Medicine, https://search.credoreference.com/content/entry/hmmedicaldict/allogeneic_also_allogenic/0 (accessed March 29, 2022).
[3] Ding, Dah-Ching, et al., Mesenchymal Stem Cells, CELL TRANSPLANT 20(1):5–14 (2011).

"A cross section of a human umbilical cord is shown in FIG. 1, which shows the umbilical artery (UA), the umbilical veins (UV), the Wharton's Jelly (WJ), and the subepithelial layer (SL)." *Id.* at 7:62–65.

After extraction, the cells of the SL are placed on a substrate, which can be a solid or semi-solid material. *Id.* at 8:39–9:3. The SL is then "cultured in a suitable medium . . . for a period of time sufficient to establish primary cell cultures. (e.g. 3-7 days in some cases)." *Id.* at 9:16–18. The SL tissue is then removed and discarded, and the cells are further cultured and expanded in larger culture flasks in "either a normoxic or hypoxic culture conditions." *Id.* at 9:19–22.

Example 2 of the '176 patent describes one method of cell extraction and culturing:

> Culturing Cells or Stem Cell from Umbilical Cord for Clinical Use
>
> Umbilical cord tissue is obtained and maternal blood is tested for infectious disease prior to derivation of cell and stem cell populations. A 1 cm piece of cord is washed 10 times in a solution of DPBS containing 10% PRP-Lysate or platelet lysate. The umbilical cord is then opened longitudinally to expose the interior of the umbilical cord. All tissue is removed that can give rise to endothelial cells. The umbilical cord is then place [sic, placed] directly into a cell culture dish containing Media Composition-1 with the interior of the umbilical cord in contact with the plastic and cultured in either normoxic or hypoxic culture environments.
>
> On the third day the media is replaced with fresh Media Composition-1 and cultured until day seven when the explants are removed for primary cell expansion. The cells are fed every other day until approximately 500,000-1,000,000 cells can be harvested and further expanded. It is noted that the media used for subsequent examples is Media Composition-1 unless specifically noted otherwise.

Id. at 13:50–14:5 (Media Composition-1 is described at 13:31–48).

After culture is established, the cells can "be utilized as-is upon isolation from the SL tissue" or can be "differentiated into other cell types . . . by exposing the cells to chemicals, growth factors, supernatants, synthetic or naturally occurring compounds, or any other agent capable of transforming the cells." *Id.* at 10:55–65.

The '176 patent discloses that cells isolated from the SL tissue "can have a variety of characteristic markers[4] that distinguish them from cell[s] previously isolated from umbilical cord samples." *Id.* at 7:65–67. Cells isolated from SL tissue are disclosed to have the following genetic characteristics, as defined by their cell markers: i.e., they "are positive for SOX2 and OCT4, and are negative for NANOG as compared to control cells" and also "are positive for CD44[,] . . . CD90[, and] CD146." *Id.* at 9:53–60; *see also id.* at 8:3–33 (providing "[v]arious cellular markers that are either present or absent [that] can be utilized in the identification of these SL-derived cells").

[4] A "genetic marker" or "cell marker" is "a readily recognizable genetic trait, gene, DNA segment, or gene product used for identification purposes especially when closely linked to a trait or to genetic material that is difficult to identify." Merriam Webster dictionary: https://www.merriam-webster.com/dictionary/genetic%20marker#medicalDictionary (accessed April 13, 2022). Ex. 3003. This definition is not disputed by the parties.

E. Illustrative Claim

Petitioner challenges claims 1–15 of the '176 patent. Pet. 7. Claim 1 is independent and claims 2–15 depend from claim 1. Ex. 1001, 19:5–20:28. Claim 1 is illustrative of the claimed subject matter and is reproduced below.

> 1. An isolated cell prepared by a process comprising:
> placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate; and
> culturing the subepithelial layer such that the isolated cell from the subepithelial layer is capable of self-renewal and culture expansion,
> wherein the isolated cell expresses at least three cell markers selected from the group consisting of CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, or CD105, and
> wherein the isolated cell does not express NANOG and at least five cell markers selected from the group consisting of CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR.

Claims 1–9 and 11–15 recite isolated cells with various characteristics or culture environments, and claim 10 recites a culture of differentiated cells derived from the isolated cell of claim 1. *Id.* at 19:20–20:28.

F. Prior Art and Asserted Grounds

Petitioner asserts that the Challenged Claims are unpatentable based on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–13, 15	102[5]	Majore[6]
2	14	103	Majore, Mistry[7]
3	1–13, 15	103	Majore, Pierantozzi,[8] Rojewski,[9] Meiron,[10] Riekstina[11]
4	14	103	Majore, Pierantozzi, Rojewski, Meiron, Mistry
5	1–15	103	Phan,[12] Pierantozzi,

[5] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the '176 patent claims priority to a provisional application filed prior to the effective date of these AIA amendments, and there is no dispute over priority date, we apply the pre-AIA version of 35 U.S.C. § 102 and § 103.

[6] Ingrida Majore, et al., *Growth and Differentiation Properties of Mesenchymal Stromal Cell Populations Derived from Whole Human Umbilical Cord*, STEM CELL REV. AND REP. 7:17–31 (2011) (Ex. 1011, "Majore").

[7] Sanjay Mistry, et al, U.S. Pat. No. US 7,510,873 B2, issued Mar. 31, 2009 (Ex. 1015, "Mistry").

[8] Enrico Pierantozzi, et al., *Pluripotency Regulators in Human Mesenchymal Stem Cells: Expression of NANOG But Not of OCT-4 and SOX-2*, STEM CELLS AND DEV. 20(5):915–923 (2011) (Ex. 1012, "Pierantozzi").

[9] Markus Thomas Rojewski, et al., *Phenotypic Characterization of Mesenchymal Stem Cells from Various Tissues*, TRANSFUS. MED. HEMOTHER., 35:168–184 (2008) (Ex. 1014, "Rojewski").

[10] Moran Meiron, et al., WO 2009/037690 Al, published March 26, 2009 (Ex. 1016, "Meiron").

[11] Una Riekstina, et al., *Embryonic Stem Cell Marker Expression Pattern in Human Mesenchymal Stem Cells Derived from Bone Marrow, Adipose Tissue, Heart and Dermis,* STEM CELL REV. AND REP. 5:378–386 (2009) (Ex. 1013, "Riekstina").

[12] Toan-Thang Phan and Ivor Jiun Lim, WO 2006/019357 Al, published February 23, 2006 (Ex. 1017, "Phan").

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
			Rojewski, Meiron, Riekstina
6	1–8, 10–13, 15	103	Kita,[13] Pierantozzi, Rojewski, Meiron, Riekstina
7	14	103	Kita, Pierantozzi, Rojewski, Meiron, Riekstina, Mistry
8	9	103	Kita, Pierantozzi, Rojewski, Meiron, Majore

Pet. 7. Petitioner alleges "all of the cited references qualify as prior art even if the challenged claims were found to be entitled to the filing date of the first provisional application" and provides evidence of the public availability of these references. *Id.* at 3–6. Patent Owner does not challenge the prior art status of any asserted reference. *See generally* PO Resp.

In support of its Petition, Petitioner relies on the supporting First and Second Declarations of its expert Scott Olson, Ph.D. Ex. 1007 ("First Olson Dec."), Ex. 1089 ("Second Olson Dec."). Patent Owner relies on the supporting declarations of inventor Amit Patel, M.D. (Ex. 2009); 2017 Rule 132 Declaration of Applicant Dr. Amit Patel (Ex. 2011); and the expert declarations of Camillo Ricordi, M.D. (Ex. 2002), Kristine Krafts, M.D. (Ex. 2017), and Scott Burger, M.D. (Exs. 2022, 2027).

[13] Katsuhiro Kita, et al., *Isolation and Characterization of Mesenchymal Stem Cells From the Sub-Amniotic Human Umbilical Cord Lining Membrane*, STEM CELLS AND DEV. 19(4):491–501 (2009) (Ex. 1010, "Kita").

II. ANALYSIS

A. Legal Standards

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")).

"A claim is anticipated [under 35 U.S.C. § 102] only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987). "A reference may anticipate inherently if a claim limitation that is not expressly disclosed 'is necessarily present, or inherent, in the single anticipating reference.' The inherent result must inevitably result from the disclosed steps; '[i]nherency . . . may not be established by probabilities or possibilities.'" *In re Montgomery*, 677 F.3d 1375, 1379–80 (Fed. Cir. 2012) (citations omitted, alterations in original). Whether a reference anticipates is assessed from the perspective of an ordinarily skilled artisan. *See Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003).

A patent claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). In *Graham v. John Deere Co.*, 383 U.S. 1 (1966), the Supreme

Court set out a framework for assessing obviousness under § 103 that requires consideration of four factors: (1) the "level of ordinary skill in the pertinent art," (2) the "scope and content of the prior art," (3) the "differences between the prior art and the claims at issue," and (4) "secondary considerations" (or "objective indicia")[14] of nonobviousness such as "commercial success, long felt but unsolved needs, failure of others, etc." *Id.* at 17–18; *KSR*, 550 U.S. at 407.

Where the challenged claim is a product-by-process claim, analysis of patentability focuses on the product:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. . . .
>
> The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.

[14] Patent Owner has presented objective indicia evidence to support non-obviousness in this processing. *See* PO Resp. 66–69. However, because we determine that Petitioner has not met its burden to establish obviousness under the first three Graham factors, we need not address this objective indicia evidence. *See Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("Because we agree with the district court that the Defendants failed to prove that claim 12 of the '528 patent would have been prima facie obvious over the asserted prior art compounds, we need not address the court's findings regarding objective evidence of nonobviousness."); *ProBatter Sports, LLC v. Sports Tutor, Inc.*, 680 Fed.Appx. 972, 976 (Fed. Cir. 2017) ("Because we conclude that Sports Tutor failed to establish obviousness by clear and convincing evidence even without considering ProBatter's contrary evidence, we need not address ProBatter's evidence of objective indicia of nonobviousness.").

In re Thorpe, 777 F.2d 695, 698 (Fed. Cir. 1985) (citations omitted). *See also Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1370 n.14 (Fed. Cir. 2009) ("Because validity is determined based on the requirements of patentability, a patent is invalid if a product made by the process recited in a product-by-process claim is anticipated by or obvious from prior art products, even if those prior art products are made by different processes."); *see also Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345 (Fed. Cir. 2016).

B. Level of Ordinary Skill in the Art

"The level of skill in the art is a factual determination" that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham*, 383 U.S. at 17–18); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art ("skilled artisan") at the time of the invention would have had

> at least a doctorate degree in cell biology, molecular biology, or a similar field with at least three years of experience in research relating to umbilical cord stem cells, or an Bachelor's degree in cell biology, molecular biology, or a similar field, with approximately 10 years of experience relating to umbilical cord stem cells. . . . Additional education might substitute for experience, while significant experience in the field of umbilical cord stem cell biology or post-natal tissue-derived stem cell biology might substitute for formal education.

Pet. 15 (citing Ex. 1007 ¶¶ 19–24). Patent Owner does not comment on the characterization offered by Petitioner or offer one of its own. *See generally* PO Resp.

In our Institution Decision, we found Petitioner's characterization consistent with the level of skill in the art at the time of the invention as reflected by the '176 patent and the cited prior art, and adopted it. Inst. Dec. 11. Neither party further addressed the level of skill in subsequent briefing. We find no reason to disturb our original analysis and continue to apply Petitioner's characterization herein. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

C. Weight to Give Expert Testimony

Patent Owner argues that Dr. Olson's declaration testimony should be excluded in its entirety, or, in the alternative, that ¶¶ 92–234 of Dr. Olson's First Declaration (Ex. 1007) and ¶¶ 25–87 of his Second Declaration (Ex. 1089) should be excluded "as improper expert testimony under FRE 702–703." Patent Owner's Motion to Exclude Evidence (Paper 29, "PO MTE"), 1. Patent Owner argues that "most of Dr. Olson's opinions, if not all, are tethered to the facts only by the 'say so' of Olson." *Id.* at 3. Patent Owner identifies six examples of testimony proffered by Dr. Olson that Patent Owner argues are unsupported by data, even where Dr. Olson could have generated his own data to support his position. *Id.* at 3–15. Patent Owner also argues that Dr. Olson's own deposition testimony and the evidence of record contradicts Dr. Olson's declaration testimony. *Id.* at 6, 8. Patent Owner argues that Dr. Olson's declaration testimony, particularly his Second

Declaration, merely parrots Petitioner's arguments without independent analysis, and that certain opinions are demonstrably false. *Id.* at 12–15.

Petitioner responds that Patent Owner's motion does not properly challenge Dr. Olson's expert declarations, but instead attempts to argue the weight of the evidence. Petitioner's Opposition to Patent Owner's Motion to Exclude (Paper 36, "Pet. Opp. MTE"), 1–7. Petitioner contends that Dr. Olson's opinions are founded on the '176 patent and the prior art references. *Id.* at 7. Petitioner argues that the Board has discretion and is able to consider the evidence. *Id.* at 2.

Patent Owner replies that Petitioner's response does not address the factual insufficiencies in Dr. Olson's testimony. Patent Owner's Reply in Support of its Motion to Exclude Evidence (Paper 37, "PO MTE Reply"), 1. Patent Owner reiterates the bases for its motion for exclusion and argues that Petitioner did not show where the '176 patent and prior art or other record evidence supported Dr. Olson's opinions, leaving them "neither scientifically sound nor reliable." *Id.* at 2–5.

We begin by assessing Dr. Olson's ability to testify as to the level of skill in the art. A witness offering expert testimony as to the understanding of one of ordinary skill in the art must have at least ordinary skill to provide relevant and reliable testimony that is helpful to the factfinder. *Kyocera Senco Indus. Tools, Inc. v. ITC*, 22 F.4th 1369, 1376–77 (Fed. Cir. 2022). Dr. Olson has a Bachelor's of Science degree in Biochemistry and a Ph.D. in Interdisciplinary Molecular and Cellular Biology. Ex. 1003 ¶ 9. Dr. Olson has studied adult stem/progenitor cells for 19 years and has published 30 research papers on mesenchymal stromal cells (MSCs). *Id.* ¶¶ 8, 11. We find this level of skill meets the qualifications for the level of ordinary skill

in the art under the training and experience portion of the definition we have adopted for purposes of this opinion (see § II.B.). Accordingly, we find Dr. Olson qualified to opine on the level of ordinary skill with regard to issues of umbilical cord stem cells, including mesenchymal stromal cells and molecular and cellular biology techniques used to cultivate them.

We now turn to the substance of Patent Owner's Motion to Exclude Dr. Olson's testimony. Patent Owner asks us to exclude the declarations in their entirety, or certain sections defined by numbered paragraphs. PO MTE 1. We begin by examining the subject paragraphs, ¶¶ 92–234 of Dr. Olson's First Declaration and ¶¶ 25–87 of his Second Declaration. This testimony largely provides the basis for Dr. Olson's opinions on unpatentability of the Challenged Claims. Included within the large span of the First Declaration that Patent Owner seeks to exclude are paragraphs describing the processes used in the prior art references and results obtained from those prior art processes, without corresponding opinion testimony as to what limitations the references teach or whether they anticipate or render the Challenged Claims obvious. *See, e.g.*, Ex. 1003 ¶¶ 92, 95, 99, 128–130, 134, 138, 141, 143, 151, 155, 186, 187, 190, 192, 203–207, 209, 219, 230. The challenged testimony also contains other explanatory material that we find helpful in understanding the prior art references. *See, e.g.*, Ex. 1003 ¶¶ 110, 119, 231. It also contains an analysis of the opposing expert's testimony and reasoning. *See* Ex. 1089 ¶¶ 28–31, 57–59, 74. In short, we find Patent Owner's Motion to Exclude overreaches in attempting to exclude testimony that is helpful to the trier of fact and in broadly characterizing Dr. Olson's analysis as entirely without basis.

"The Board has broad discretion to assign weight to be accorded expert testimony." Consolidated Trial Practice Guide 35 (available at https://www.uspto.gov/TrialPracticeGuideConsolidated) ("CTPG"). In reviewing and according weight to Dr. Olson's testimony, as well as the testimony provided by the other experts in this proceeding, Dr. Krafts, Dr. Ricordi, and Dr. Burger, we have separately considered whether each aspect of their testimony is supported by the disclosures of the prior art references, the challenged patent, and other evidence of record. *See Elbit Sys. of Am., LLC v. Thales Visionix, Inc.*, 881 F.3d 1354, 1358 (Fed. Cir. 2018) ("The [Patent Trial and Appeal Board ('PTAB')] [i]s entitled to weigh the credibility of the witnesses."); *Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1041 (Fed. Cir. 2017) ("To the extent [a party] challenges the PTAB's factual findings, . . . the PTAB is permitted to weigh expert testimony and other record evidence and, in so doing, rely on certain portions of an expert's declaration while disregarding others."). In so doing, we may accord an expert's testimony little weight when it contains an exact and conclusory restatement of the petition's arguments without any additional supporting evidence or reasoning. *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15–16 (PTAB Aug. 24, 2022)) (Decision Denying Institution) (precedential) (finding that expert's conclusory assertions that repeat the proposition for which they are offered without "any additional supporting evidence or provide any technical reasoning" in support are "conclusory and unsupported, add little to the conclusory assertion[s] for which [they are] offered to support, and [are] entitled to little weight"); *see also* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled

to little or no weight."); *Upjohn Co. v. Mova Pharm. Corp.*, 225 F.3d 1306, 1311 (Fed. Cir. 2000) ("Lack of factual support for expert opinion going to factual determinations, however, may render the testimony of little probative value in a validity determination.") (quoting *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985)). We therefore deny Patent Owner's Motion to Exclude, but consider the critiques of Dr. Olson's testimony as we analyze Petitioner's grounds.

D. Claim Interpretation

We apply the same claim interpretation standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.100(b). Under that standard, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). "In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" *Phillips*, 415 F.3d at 1317.

The parties proposed multiple terms for construction. Pet. 16–20; PO Resp. 7–14. On the current record, and in view of the disputed issues, we need only interpret "placing a sub-epithelial layer . . . in direct contact with a growth substrate," and "expresses/does not express" to render our judgment. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361

(Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

1. "placing a sub-epithelial layer . . . in direct contact with a growth substrate"

Petitioner argues that "direct contact with a growth substrate" should be interpreted to mean "direct contact with any material capable of being used to obtain explants." Pet. 18–19 (citing Ex. 1001, 2:29–30; 8:62–64); Ex. 1007 ¶ 71. Petitioner points to disclosures in the '176 patent that teach "[a] variety of techniques can be utilized to extract the isolated cells of the present disclosure from the SL, and any such technique that allows such extraction without significant damage to the cells is considered to be within the present scope." Ex. 1001, 8:34–39; Pet. 16; Pet. Reply 3.

Patent Owner contends that "placing a sub-epithelial layer . . . in direct contact with a growth substrate" should be interpreted to mean "placing the exposed subepithelial layer of an umbilical cord interior side down such that the exposed subepithelial layer is in direct contact with the growth substrate" (hereafter the "interior side down" embodiment). PO Resp. 7–8. Patent Owner cites the Specification at 8:51–54 and inventor Dr. Patel's 2017 Declaration in which he specifies that, in his isolated cell preparation method, the "[u]mbilical cord tissue . . . placed interior side down such that the subepithelial layer was in contact with the growth substrate." Ex. 2011 ¶ 6. Patent Owner argues "placing" requires intentional action and that its interpretation of "placing . . . in direct contact with a growth substrate" supports contacting the subepithelial layer interior side down. PO Resp. 8.

At oral argument, Patent Owner's counsel conceded that of the multiple embodiments in the Specification, its proposed interpretation is supported by the particular embodiment disclosed at paragraph 8, lines 39–54:

> the umbilical cord is cut open; the Wharton's jelly is removed, and, quote, the remaining umbilical cord tissue can then be placed interior side down on a substrate such that an interior side of the SL, of subepithelial layer, is in direct contact with the substrate.

Tr. 33:21–34:15 (referencing Ex. 1001, 8:39–54).

Petitioner replies that, despite this exemplary embodiment, the '176 patent does not require any specific orientation and "does ***not disclose anywhere*** that the SL ***must*** be placed interior side down." Pet. Reply 4 (citing Ex. 1089 ¶¶ 7–9). Petitioner argues that the phrase "direct contact" is broader than interior side down orientation, and that Patent Owner's expert conceded this in deposition. *Id.* (citing Ex. 1083, 236:12–237:23). Petitioner argues that the scope of the '176 patent's Specification is inconsistent with Patent Owner's proposed definition and its expert's interpretation. *Id.* at 5. Petitioner cites Dr. Burger's testimony that making an isolated cell according to the patent would not include growing MSCs in a tissue culture flask because placing the subepithelial layer requires a flat, stable surface and a tissue culture flask can be moved. *Id.* (citing Ex. 1083, 61:20–62:9). Petitioner argues that Patent Owner's position is wrong because the Specification does not disavow any claim scope for the claims at issue. *Id.* (citing *Continental Circuits LLC v. Intel Corp.*, 915 F.3d 788, 796–97 (Fed. Cir. 2019)).

Patent Owner acknowledges that the Specification is broader than the claims at issue, and cites cases supporting its argument that the claims can

nevertheless be more limited where they focus on certain embodiments. PO Sur-Reply 18–19 (citing *ScriptPro LLC v. Innovation Assocs.*, 833 F.3d 1336, 1341–42 (Fed. Cir. 2016); *E-Pass Techs., Inc. v. 3Com Corp.*, 343 F.3d 1364, 1370 (Fed. Cir. 2003); and *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985)).

Beginning with the language of claim 1, we examine the surrounding phrases within the claim that give context to the term at issue: "An isolated cell prepared by a process comprising placing a subepithelial layer of mammalian umbilical cord tissue in direct contact with a growth substrate; and culturing the subepithelial layer . . ." Because the purpose of the recited process is to culture the cells, we interpret "placing a subepithelial layer of umbilical cord tissue in direct contact with a growth substrate" as meaning "to intentionally place umbilical cord tissue comprising the subepithelial layer so that it touches a growth substrate to permit cell culture."

Turning to the Specification, we find that the disclosures of "subepithelial layer" do not uniformly require its isolation from the umbilical cord or removing Wharton's jelly prior to the "placing" step. *See, e.g.*, Ex. 1001, 2:19–20 ("*[i]n one aspect*, dissecting the subepithelial layer *further includes* removing Wharton's Jelly from the umbilical cord"); 2:21–23 ("[t]he subepithelial layer can be cultured in any media capable of producing explants therefrom, and any such medium is considered to be within the present scope"); 8:34–39 ("[a] variety of techniques can be utilized to extract the isolated cells of the present disclosure from the SL, and any such technique that allows such extraction without significant damage to the cells is considered to be within the present scope").

We acknowledge that the embodiment disclosed in the Specification at 8:39–58 discloses dissecting the subepithelial layer from the umbilical cord, washing it to remove Wharton's jelly, and placing it interior side down on a substrate, either whole or in pieces. But this embodiment is narrower than the remainder of the disclosure, discussed above, which does not require isolation of the subepithelial layer or removal of Wharton's jelly. "[T]here is a strong presumption against a claim construction that excludes a disclosed embodiment." *See Nobel Biocare Svcs. AG v. Instradent USA*, 903 F.3d 1365, 1381 (Fed. Cir. 2018) (quoting *In re Katz Interactive Call Processing Patent Litig.*, 639 F.3d 1303, 1324 (Fed. Cir. 2011)). While our reviewing court has observed that "[i]t is often the case that different claims are directed to and cover different disclosed embodiments," it has also "cautioned against interpreting a claim term in a way that excludes disclosed embodiments, when that term has multiple ordinary meanings consistent with the intrinsic record." *Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1383 (Fed. Cir. 2008); *see also Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1305 (Fed. Cir. 2007) ("We normally do not interpret claim terms in a way that excludes disclosed examples in the specification.").

Here, "placing a subepithelial layer of umbilical cord tissue in direct contact with a growth substrate" can be interpreted consistently with the intrinsic record to cover multiple embodiments. Patent Owner has offered no clear disavowal of claim scope or evidence of broader claims in a parent application that would support interpretation of claim 1 to cover a narrower embodiment only. *See iRobot Corp. v. ITC*, 767 F. App'x 944, 947–48 (Fed. Cir. 2019) (finding claims did not need to be coextensive with specification

where parent claim contained "claims relating to a breadth of embodiments" and the continuation-in-part (CIP) application at issue contained narrower claims directed to a single embodiment).

The same principles apply to "direct contact." The purpose of the process is to culture cells, and claim 1 instructs that the subepithelial layer must be "in direct contact." Ex. 1001, 19:6–7. But the Specification does not specify the orientation in all embodiments when discussing placing the subepithelial layer on the culture substrate, and in some instances indicates that culture occurs without interior side down contact. *See id*. at 2:9–17 (describing method that "can include" dissecting subepithelial layer from umbilical cord and placing it interior side down);); 2:29–36 (substrate used for culture can be any substrate capable of deriving explants and subepithelial layer can be plac)ed on it without additional pretreatment); and 2:37–40 ("[a]ny type of semi-solid substrate that is capable of supporting the subepithelial layer during the culturing procedure is considered to be within the present scope"). The sole use of "direct contact" is in claim 1. Patent Owner has provided no evidence of claim disavowal that would lead us to conclude that the Challenged Claims are properly drawn to a portion of the Specification and should be interpreted to require an interior side down orientation.

Patent Owner's cited cases do not persuade us that the claims can nevertheless be more limited where they focus on certain embodiments. *See* PO Sur-Reply 18–19. In *ScriptPro*, the invention related to a "collating unit" used with a control center and an automatic dispensing system to store prescription containers after a medication has been dispensed into the containers. 833 F.3d at 1338. The Federal Circuit addressed "whether the

'601 patent's specification limits the invention to a collating unit that sorts and stores prescription containers by patient-identifying information and slot availability." *Id.* The district court had found the asserted claims invalid under 35 U.S.C. § 112 for lack of written description because the claim scope was broader than the specification. *Id.* On review, the Federal Circuit reversed and held that the specification did not limit the claimed invention because the patent in question disclosed multiple problems that the invention could solve, including other sorting methods not linked to patient-identifying information. *Id.* at 1340–41. *ScriptPro* does not apply here because Patent Owner here asks us to construe the term *more narrowly* than the full scope the Specification teaches, not to find that a broad claim is limited by the disclosure of the specification.

In *E-Pass*, the patent at issue disclosed a method and device for substituting a single electronic multifunction card for multiple credit cards. 343 F.3d at 1365. In construing the claim terms, the district court required that the "multi-function card" operate as a single purpose card, and interpreted the claim to cover only a card of the size that would fit within an ATM terminal, to allow the multifunction card to be interchangeable with a credit card. *Id.* at 1366–67. On review, the Federal Circuit found the district court should have interpreted the claim according to its plain meaning absent evidence that the patentee acted as its own lexicographer in defining terms or clearly disclaimed coverage during prosecution. *Id.* at 1369. Here, Patent Owner has done neither. Patent Owner could have written the claim to recite "an *isolated* subepithelial layer," which would have distinguished the recited claim from embodiments covering cut sections of umbilical cord, but did not. And as described above, Patent Owner did not disclaim any scope

for the "direct contact" limitation of claim 1 or identify broader claims that were once pending in a parent application.

We likewise find *SRI* does not alter our assessment. The section cited by Patent Owner states general claim construction principles, including that claims are interpreted in light of the specification and that not everything expressed in the specification need be read into all the claims. 775 F.2d at 1121. *SRI* does not apply the cited principle, but instead resolves the claim interpretation issue on the basis of claim differentiation. *Id*. at 1121.

Patent Owner did not disclaim any scope for the Challenged Claims. Claim 1 is independent and claim differentiation does not apply. Not all instances of the Specification disclose isolation of the subepithelial layer. We therefore construe "placing a subepithelial layer of umbilical cord tissue in direct contact with a growth substrate" consistent with its plain meaning and generally consistent with Petitioner's arguments as "orienting umbilical cord tissue comprising the subepithelial layer such that the subepithelial layer touches a growth substrate to permit culturing." Because the Specification does not disclose only embodiments in which the subepithelial layer alone is isolated before culturing, or expressly require that the interior side down of the subepithelial layer is placed onto the culture medium, we decline to import those limitations into the claims.[15]

[15] *See also* Ex. 1089 ¶ 18, in which Dr. Olson testifies that it would be "extremely challenging" to remove all Wharton's jelly from the SL and the methods of the '176 patent would not accomplish this; Ex. 2027 ¶ 39; Ex. 1083, 277:24–278:14; 282:5–12 (Dr. Burger acknowledging removing Wharton's jelly is challenging).

2. expresses/does not express

Petitioner proposes that "expresses" "[a]s it pertains to biological markers means that the marker is detected above the level of a negative control." Pet. 18. Petitioner relies on Dr. Olson's testimony that marker expression can be measured by qualitative or quantitative means, and is compared against a negative control to distinguish detection or lack of detection from background noise. *Id.* at 17–18 (citing Ex. 1007 ¶ 69).

Patent Owner proposes that "expresses" means "the marker is detected above the level of a negative control in a significantly high percentage of the isolated cells tested." PO Resp. 12. Patent Owner relies on the testimony of Dr. Burger that the term must be read in context with "culturing" and "self-renewal and culture expansion" by interpreting the claims in a manner that accounts for the purity of the cells. *Id.* at 12–13 (citing Ex. 2022 ¶¶ 88–94).

Petitioner argues Patent Owner's definition is ambiguous because it lacks a metric for determining a "significantly high percentage of cells" and cites Dr. Burger's testimony acknowledging that determining whether cells are positive for a given marker "depends on the cell and the marker" and that what "significantly" means may vary. Pet. Reply 7–18 (citing Ex. 1083, 250:10–20, 252:10–19, 252:20–253:9, 256:18–257:10. Petitioner notes that Dr. Burger agreed that the '176 patent did not disclose a way to determine whether markers were positive or negative including how to assess for a "significantly high percentage of cells." *Id.* at 8 (citing Ex. 1083, 250:21–252:19; 253:10–19; 255:6–257:10).

Patent Owner responds that the skilled artisan and Petitioner's own experts understand "expression or non-expression of surface markers in

terms of cell populations." PO Sur-reply 20 (citing Ex. 1007 ¶¶ 49, 53 and Ex. 1085, 24:18–25). Patent Owner notes that Dr. Olson testified that determining whether a surface marker is expressed depends on the situation, the markers, the controls, and the measurements. *Id.* at 21 (citing Ex. 2034, 30:21–31:12; 32:5–17; 36:17–37:16).

Claim 1 recites that the isolated cell 1) does not express NANOG; 2) expresses at least three of markers CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, and CD105; and 3) does not express at least five of the markers CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, and HLA-DR. Aside from identifying the cell markers that the isolated cell does and does not express, claim 1 does not provide any further information about what "expresses" means.

Turning to intrinsic evidence, we note neither party has cited relevant prosecution history. The Specification does not elaborate on how expression is analyzed, but discloses that the markers are used to "distinguish [the isolated cells] from cell[s] previously isolated from umbilical cord samples" and that "[v]arious cellular markers that are either present or absent can be utilized in the identification of these SL-derived cells, and as such, can be used to show the novelty of the isolated cells." Ex. 1001, 7:65–8:6.

Because the intrinsic evidence does not permit us to define with particularity how the ordinarily skilled artisan would have assessed a positive or negative result, as is necessary to assess the asserted prior art, we review the expert testimony for guidance on what an ordinarily skilled artisan would have understood regarding how to confirm whether an isolated cell expresses/does not express the markers of claim 1. Both experts agree that, at the time of the invention, marker analysis was performed at a cell

population level. *See* Ex. 2034, 34:3–6; Ex. 2022 ¶¶ 88, 89, 91 ("expresses" refers to "the fraction of the population of tested cells that express a marker" as shown in the '176 patent Specification, which tested plural cells; ISCT criteria specify that "≥95% of the MSC population must express [three markers,] CD105, CD73 and CD90, as measured by flow cytometry," to qualify as MSCs (alteration in original)); Ex. 1083, 103:18–105:20 (Dr. Burger describing how expression is determined on a population of cells using flow cytometry); Ex. 1089 ¶ 23 (Dr. Olson describing testing cells in a population for markers against positive and negative controls).

Dr. Olson opines that the cell markers recited in the '176 patent are "common surface markers used to characterize native or expanded MSCs from various tissues and have known biological functions" and that their expression or non-expression patterns "would be expected in "'stromal cells'" generally, of which MSCs are one type" but that heterogeneity of expression of markers could be affected by "variability in, inter alia, isolation procedure, in vitro culturing conditions, and marker detection methods, even when the MSCs are derived from the same tissue." Ex. 1007 ¶ 56.

Dr. Burger clarifies that the figures of the '176 patent exemplify expression and non-expression patterns of the claimed "isolated cell" based on marker expression of multiple cells. Ex. 2022 ¶ 89. Dr. Burger references ISCT criteria[16] as exemplifying expression as "≥95% of the MSC

[16] The International Society for Cellular Therapy is "a global society of clinicians, regulators, researchers, technologists, and industry partners with a shared vision to translate cell and gene therapy into safe and effective therapies to improve patients' lives worldwide." *See* https://www.isctglobal.org/about/about-us (accessed March 30, 2023)

population must express [three markers,] CD105, CD73 and CD90, as measured by flow cytometry" and non-expression "≤2%" of cells testing positive for the specified markers." Ex. 2022 ¶ 91 (alteration in original).

Briefly considering the asserted prior art (solely for purposes of determining how the term "express" was used in the art), the references use multiple methods including quantification of data from immunofluorescence microscopy and RT-PCR[17] analysis relative to positive and negative controls to assess expression patterns. *See, e.g.*, Ex. 1010, 494–95; Ex. 1013, 384, Fig. 3. Considering this information together, and consistent with our interpretation of "isolated cell" as indicating a cell population and generally consistent with Petitioner's proposed interpretation, we interpret "expresses" to mean that "the marker is confirmed present relative to a control sample," and that "does not express" means that "the marker is confirmed absent relative to a control sample." and that "does not express" means that "the marker is confirmed absent relative to a control sample." Using such techniques, evidence of expression or non-expression patterns as recited in the Challenged Claims can be used to identify and distinguish the isolated cell population from other cell populations.[18]

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[17] RT-PCR is reverse transcription polymerase chain reaction analysis.
[18] We note that both experts agree that expression and non-expression can be influenced by factors such as culture conditions and cell-to-cell interactions. *See, e.g.*, Ex. 1003 ¶ 49 ("the MSCs isolated from umbilical cord tissues were heterogeneous with respect to primitive marker expression (e.g., Oct-4, Nanog, Sox-2, or SSEA-4) and that the marker expression could turn on or off depending on culture conditions"); Ex. 2027 ¶ 30 ("Gene expression, including expression of genes for cell markers, is affected by many factors including, but without limitation, senescence, the cell-to-cell interaction facilitated by the proximity of other tissues or cells, or other biochemical signals or proteins that trigger changes in gene expression."). Despite these

We determine that no other interpretation of any claim term is necessary. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (holding that only terms in controversy must be construed and only to the extent necessary to resolve the controversy) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

E. Ground 1– Anticipation of Claims 1–13, and 15 by Majore

1. Majore (Ex. 1011)

Majore discloses isolating mesenchymal stem cells (MSC) from human umbilical cord (UC) tissue to create highly proliferative isolated cells. Ex. 1011, 17. Majore discloses that "cells isolated from whole UC satisfies [sic] all requirements essential for the generation of stem cell banks containing permanently available cell material for applications in the field of regenerative medicine." *Id.*

Majore describes a method for isolation of MSCs as follows:

> For cell isolation from whole UC an explant culture approach was employed. Human UCs (MK 240707, HD 140509, NS 010408, NS 190109) were obtained from term delivery (38–40 weeks) by Cesarean section patients (n=4) . . . Blood from UC vessels was removed and the UC was placed in PBS (phosphate buffered saline) enriched with 5 g/l glucose (Sigma Aldrich), 50 µg/ml gentamicine (PAA Laboratories), 2.5 µg/ml amphotericin B (Sigma Aldrich), 100 U/ml penicillin and 100 µg/ml streptomycin (PAA Laboratories). At the laboratory UC was

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known influences, the '176 patent provides no guidance regarding how to assess expression or non-expression for purposes of distinguishing the claimed isolated cell from other MSCs. *See* Ex. 1089 ¶ 20 ("the '176 patent does not mention any factor that could change marker expression, such as the media or culture conditions, and does not describe or claim unique tissue culture conditions or media to achieve any desired result").

> cut into approx. 10 cm large segments which further were minced in ca. 0.5 cm^3 large pieces and placed in 175-cm^2 tissue culture flasks (Sarstedt). Then these pieces were incubated in αMEM (Invitrogen) enriched with 15% of allologous human serum . . . A beginning outgrowth of an adherent cell layer from single tissue pieces was observed after approx. 10 days. After 2 weeks, the tissue pieces were removed and the adherent cells were harvested . . . Cells were subcultured at the density of 4.000 cells/cm^2 in 175-cm^2 tissue culture flasks and grown until 80% of confluence. Subsequently cells were harvested as already described and used for immunophenotype analysis or cryopreserved.

Id. at 18. Majore discloses that immunophenotype analysis detected cell surface markers CD34, CD73, CD90, and CD105 in the isolated cells. *Id.* at 22 (Table 2). Majore further discloses that no "xenogenic[19] media supplements during UC cell isolation, expansion and differentiation." *Id.* at 28.

2. Analysis

a) Claim 1

Petitioner asserts that Majore inherently[20] discloses the limitations of claim 1 because its disclosed method of inducing stem cells to grow from umbilical cord tissue "necessarily includes the subepithelial layer of the

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[19] "Xenogenic" means "derived from, originating in, or being a member of another species." Dictionary.com definition of "xenogenic," found at: https://www.merriam-webster.com/dictionary/xenogeneic#medical Dictionary (accessed April 15, 2022). Ex. 3004. This definition is not disputed by the parties.

[20] Petitioner also argued that Majore expressly teaches claim 1 in the instance that the markers are not given patentable weight. *See* Pet. 23, arguing Majore only inherently teaches limitations [C] and [D]. Because we find the recited markers are limitations that must be considered, consistent with our claim construction of "expresses/does not express" above, we do not further address this argument.

umbilical cord recited by the '176 patent claims." Pet. 21–28. Petitioner's contentions are supported by the declaration testimony of Dr. Olson (Ex. 1007 ¶¶ 92–122; Ex. 1089 ¶¶ 25–44).

Patent Owner argues that Petitioner fails to meet its burden because its inherency case is based on theory, not fact. PO Resp. 27–34. Patent Owner's contentions are supported by the declaration testimony of Dr. Burger (Ex. 2022 ¶¶ 137–173; Ex. 2027 ¶¶ 28–33).

As claim 1 is a product-by-process claim, "determination of patentability is based on the product itself" and "does not depend on its method of production." *In re Thorpe*, 777 F.2d at 697. Thus, we evaluate whether the evidence of record shows, by a preponderance of the evidence, that the process of Majore would have necessarily resulted in "an isolated cell" having the marker characteristics of limitations [C], [D], and [E] recited in claim 1, despite any differences between Majore's process and the process limitations of claim 1, i.e., limitations [A] and [B] referenced above.

(1) ([Preamble[21]] and [A]) "An isolated cell prepared by a process comprising placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate"

Petitioner asserts that Majore discloses "isolating MSCs from umbilical cord tissue by placing pieces of whole umbilical cord onto the surface of a tissue culture flask." Pet. 22 (citing Ex. 1007 ¶ 95). Petitioner

[21] The parties do not dispute that the preamble's recitation of "isolated cell" serves as a limitation to claim 1 as it provides antecedent basis for its recitation later in the body of the claim. Accordingly, we treat the preamble as limiting. "When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention." *See Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003).

asserts that because Majore minced the whole umbilical cord into 0.5 cm^3 pieces, "the cubic dimensions of minced pieces necessarily result[] in at least some pieces with subepithelial layer exposed by the cut which would then be in contact with the tissue culture surface upon sinking to the bottom of the flask." *Id.* at 22–23 (citing Ex. 1007 ¶ 96). Petitioner explains that through Majore's "explant" method of isolating cells from tissues, the "cells that give rise to cultured MSCs, as defined by surface marker expression, migrate out of the umbilical cord tissue via intercellular communication to emulate a wound healing condition." *Id.* at 23. Petitioner argues that the process "would result in MSCs from the subepithelial layer migrating to the periphery of the tissue and adhering to the tissue culture vessel" and thus the Majore protocol "produces cells that necessarily and inevitably comprise the cells of the subepithelial layer." *Id.*

Patent Owner argues that Majore does not disclose limitation [A] because it is "markedly different from a culture of cells obtained solely from UC subepithelial tissue," which would not contain Wharton's jelly or epithelial tissue, and because Majore does not place the subepithelial layer interior side down in direct contact with the substrate. PO Resp. 28.

As discussed above regarding claim interpretation, we do not construe "placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate" to require placing the subepithelial layer interior side down in direct contact with the growth substrate. Both Majore and the '176 patent disclose umbilical cord tissue cut into sections and placed into environments fostering cell culture and replication. Ex. 1011, 18; Ex. 1001, 13:57–14:5. Both methods result in adherent cells growing on a plastic growth surface awash in culture media. Ex. 1011, 18; Ex. 1001,

13:57–14:5. Thus, we find Petitioner has established by a preponderance of evidence that Majore teaches limitation [A].

(2) ([B]) culturing the subepithelial layer such that the isolated cell from the subepithelial layer is capable of self-renewal and culture expansion

Petitioner asserts that Majore discloses an MSC isolation protocol and that MSCs were known to be highly proliferative somatic cells able to self-renew. Pet. 23 (citing Ex. 1007 ¶ 98).

Patent Owner argues that Petitioner has not established that the cells disclosed by Majore are MSCs, including because Majore is silent on NANOG expression, limitation [C], which is an indicator of self-renewal (the presence of NANOG indicating self-renewal). PO Resp. 28–29 (citing Ex. 2027 ¶ 26).

As Dr. Olson notes (Ex. 1007 ¶ 98), Majore discloses that its umbilical-cord derived cells are highly proliferative, including after freezing and thawing, and demonstrated expansion and differentiation. Ex. 1011, Abstract, 17, 18, 28. In addition, NANOG expression is not the sole indicator of self-renewal of cells. *See* Ex. 1007 ¶¶ 45, 48 (Dr. Olson, testifying: "At the priority date of the '176 patent, there was no set of cell markers universally accepted for identification of stem cells, much less identification of MSCs" (citing in n.22, Parker GC et al., (2005) *Stem cells: shibboleths of development, part II: toward a functional definition*. STEM CELLS AND DEV. 14:463–469 (Ex. 1070); Horwitz EM et al., (2005) *Clarification of the nomenclature for MSC: the International Society for Cellular Therapy position statement*. CYTOTHERAPY 7:393–395 (Ex. 1071))); *see also* Ex. 1014, 174 ("Although such a huge number of different surface molecules has been analyzed on MSC, there is no general guiding principle to which classes of markers are expressed on MSC.").

Because Majore discloses cells isolated from an umbilical cord that are proliferative, we find Petitioner has established by a preponderance of evidence that Majore teaches limitation [B].

(3) ([D]) wherein the isolated cell expresses at least three cell markers selected from the group consisting of CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, or CD105

([C] and [E]) wherein the isolated cell does not express NANOG and at least five cell markers selected from the group consisting of CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR

To begin, we address the issue raised in our Institution Decision of whether limitations [C] and [E] reciting the non-expression of certain markers should be treated as "negative limitations," and the burden of proving that a negative limitation is satisfied by silence in the prior art. Inst. Dec. 22 n.16 (citing *Almirall, LLC v. Amneal Pharms. LLC*, 28 F.4th 265, 273 (Fed. Cir. 2022) (determining that "it was reasonable for the Board to find that, in the context of [the prior art reference], a skilled artisan would recognize that the reference discloses a complete formulation—excluding the possibility of an additional active ingredient"), and *Novartis Pharms. Corp. v. Accord Healthcare, Inc.*, 21 F.4th 1362, 1373 (Fed. Cir. 2022) (recognizing that for negative limitations, "the disclosure must be read from the perspective of a person of skill in the art")). In the Institution Decision, we invited the parties to address this issue. *Id.*

Patent Owner argues that a prior art reference's silence on whether a marker is expressed should not be taken as an inference that the marker was nonetheless present. PO Resp. 26–27. Patent Owner relies on Dr. Burger's testimony that a lack of reporting on a marker is not evidence of either positive or negative expression:

> "[D]epending on the purpose of a research study, certain markers will be measured and others will not. There are hundreds, if not thousands, of known cell surface markers, and an investigator must decide which markers are relevant to the issue at hand." "It is, in fact, poor science to report on data that are not relevant to the author's study."

Id. at 26 (citing Ex. 2027 ¶ 7). Patent Owner argues that the reason Majore's study did not investigate NANOG expression was that the "study" did not investigate the self-renewal properties of MSCs." *Id.*

Petitioner's response does not address this issue directly, but focuses on refuting Patent Owner's arguments that the gene expression resulting from culturing conditions of tissues could differ depending on what the tissues are surrounded with and whether MSC expression can be heterogenous. Pet. Reply 9–11.

We find Dr. Burger's explanation regarding the process for testing cell surface markers is persuasive. *See also* Dr. Olson's testimony regarding screening for cell surface markers, indicating that "Majore did not independently investigate CD14, CD19, and HLA-DR." Ex. 1007 ¶ 99. Upon evaluating the evidence and considering the disclosure from the perspective of an ordinary artisan, we conclude that whether a prior art reference mentions a particular cell surface marker was expressed or not expressed correlates 1) directly to whether the cell surface marker was screened for; and 2) generally to what was tested by the investigators. Thus, given the relevant claim language and under the factual circumstances presented, we conclude that the burden of proving negative limitations [C], [D] and [E] is not satisfied by silence in the prior art, but that certain inferences can be drawn from the silence depending upon the purpose of the reported investigation, as understood by an ordinary artisan.

We now turn to the remainder of the parties' arguments regarding limitations [C], [D], and [E].

Petitioner asserts that because the cells produced by Majore necessarily comprise the same cells of the '176 patent, Majore's cells would inherently possess these features and express or not express the markers recited in [C] and [D] in the claimed pattern. Pet. 23–24 (citing Ex. 1007 ¶ 101). Petitioner argues the markers themselves should not be given patentable weight as they merely describe a property of a known composition. *Id.* at 24 (citing *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999)). Petitioner argues that even if the markers are considered, the marker expression/non-expression evidence disclosed by Majore is consistent with the markers recited in [C] and [D]. *See id.* (confirming "Majore discloses its isolated cells express CD73, CD90, CD44, and CD105, and do not express CD45 and CD34," and noting that "Majore did not independently investigate CD14, CD19, and HLA-DR, but did disclose [that] MSCs (such as those derived by Majore's protocol) are expected not to express those markers") (citing Ex. 1007 ¶ 99).

Patent Owner argues that Petitioner fails to meet its burden to show that the markers are inherently present. PO Resp. 29–30. Patent Owner argues that the claimed process steps "impart an unexpected gene marker expression to the claimed cells" due to intracellular communication. *Id.* at 16. Patent Owner relies on Dr. Burger's testimony that gene expression is affected by cell-to-cell interaction facilitated by the proximity of other tissues, cells, or biochemical signals that can trigger changes. *Id.* at 17 (citing Ex. 2027 ¶ 32). Dr. Burger testifies that a mixture of a larger number of cell types would have different interactions than a heterogenous mixture

of a single cell type. *Id.* Patent Owner notes that Dr. Olson agrees that gene expression can change, including switching NANOG production on or off, in response to tissue culture conditions or addition of a protein to the culture. *Id.* at 19 (citing Ex. 1007 ¶ 49; Ex. 2034, 42:15–17; 46:18–48:16). For this reason, Patent Owner argues that the gene expression of the cells disclosed in Majore, cultured from a mixture of minced epithelial and subepithelial tissue and Wharton's jelly, would be different from those of the '176 patent, which are "solely from subepithelial tissue." *Id.* at 18 (citing ex. 2027 ¶ 18). Patent Owner argues the claimed process steps impart unexpected gene marker expression patterns, a structural and functional difference, to the claimed isolated cells. *Id.* at 16–19 (citing Ex. 2027 ¶¶ 30, 32, 33).

To begin, we consider Petitioner's argument that the claimed cell markers should not be given patentable weight. Pet. 24. We are not persuaded because the evidence of record is that the claimed isolated cell, which does not express NANOG, is distinguishably different from other MSCs, which do express NANOG. *See* Ex. 1010, 495 ("Nanog . . . is one of the key molecules necessary for the maintenance of self renewal of SCs."). Petitioner has not provided persuasive evidence that lack of NANOG expression is a newly-appreciated property of an old composition, as the Federal Circuit did in *Atlas Powder*, such as by showing test results of existing MSCs that do not express NANOG. We therefore find that the cell marker expression/non-expression pattern distinguishes the claimed isolated cell, and is therefore limiting.

Turning to the evidence regarding marker expression, we agree with Petitioner that Majore discloses expression of four of the nine recited markers for claim limitation [D], meeting the "at least three" limitation. *See*

Ex. 1011, 22, Table 2 (reporting positive cells for cell markers CD73, CD90, CD44, and CD 105). But Petitioner's evidence does not show that Majore expressly teaches that its cells do not produce NANOG (limitation [C]). *See generally id.* With regard to the five cell markers recited in limitation [E], Majore reports cells do not express only two, CD34 and CD45 (*id.* at 22, Table 2). Thus, Majore does not expressly disclose that its cells do not express NANOG (limitation [C]) or that they do not express "at least five" of the recited cell markers in limitation [E].

We next consider Petitioner's evidence that the cells produced by Majore inherently comprise the same cells of the '176 patent because they were made by an identical process, and thus inherently disclose limitations [C] and [E]. Pet. 24–25. Petitioner's evidence in support of inherency for these remaining elements is Dr. Olson's testimony. Dr. Olson, in deposition, testified that his laboratory routinely uses the Majore protocol, but he did not provide testing evidence to confirm that cells made by this method necessarily met the non-expression criteria of limitations [C] and [E]. *See* PO Resp. 3–4 (citing Ex. 2034, 61:21–63:12). When questioned about the lack of testing data at oral argument, Petitioner's counsel responded as follows:

> [JUDGE NEWMAN:] So if -- if the comparison is possible, why did you not present evidence of that comparison?
>
> MR. FITZPATRICK: We --we've had the -- we had this discussion with our -- with our expert, and our conclusion was that it's just not -- it wasn't necessary. The conclusion was that the -- the evidence that's in the -- in the prior art references, including the fact that it clearly practices the exact same steps as the claims, that was sufficient to -- and would anticipate or render obvious the claims. That's the only reason we didn't present evidence -- our own evidence.

Tr. 15:9–19. Petitioner's remaining evidence is Dr. Olson's declaration testimony that the similarity in methods would inherently produce a cell expressing the same cell surface markers because of the similarity in the protocols. *See, e.g.*, Ex. 1007 ¶¶ 99 ("Majore did not independently investigate CD14, CD19, and HLA-DR, but did provide comment that MSCs (such as those derived by Majore's protocol) are expected not to express those markers"), 101 (stating that two of the markers of limitation [E] are disclosed as not expressed in Majore, and the rest would not be expressed "because the cells obtained by Majore's protocol necessarily and inevitably comprise **the same cells** produced by the process step of claim 1[A] and 1[B], as explained above," and that the ordinary artisan would understand this because the cells are produced by the process steps for limitations [A] and [B]).

Upon analysis of the full record, including the parties' arguments and evidence, Petitioner has not shown persuasively that Majore inherently meets the non-expression criteria of limitations [C] and [E] for multiple reasons.

As explained above, in light of our claim interpretations, we find that Majore discloses a method of producing an isolated cell by placing mammalian umbilical cord tissue in direct contact with a growth substrate and culturing those cells to create a stable cell line capable of self-renewal and culture expansion. However, Majore's process differs from at least the interior-down embodiment disclosed in the '176 patent, which Patent Owner claims is the focus of the claims at issue. PO Sur-Reply 19. The '176 patent Specification also does not address whether every disclosed embodiment or the broad process parameters disclosed therein would necessarily result in an

isolated cell with a marker profile consistent with claim 1. *See* Ex. 1001, 8:6–12, 8:29–31 (providing various marker expression profiles for disclosed aspects of cells (e.g., "*in one aspect*, the isolated cell expresses at least three cell markers selected from [lists markers], and the isolated cell does not express at least three markers selected from [lists markers] . . . *in some aspects*, the isolated cell can be positive for SOX2, OCT4, or both SOX2 and OCT4.") (emphases added)). Indeed, by specifying that the isolated cell expresses "at least three cell markers" from among the nine markers in limitation [D] and does not express "at least five cell markers" among the eleven markers recited in limitation [E], the claim language itself recognizes that cells prepared according to the process limitations of limitations [A] and [B] would not all have the exact same marker expression profile. Therefore, although Majore's disclosed process may satisfy the process limitations under our claim construction, we find that does not establish that cells produced using Majore's process would necessarily have the same marker profile required by the claim.

Petitioner has not provided any evidence that the marker expression profile is *only* dependent on the process used to produce the claimed cells.[22]

[22] Only if Petitioner had adduced evidence that the marker expression profile solely depends on the process used to produce the claimed cells could Petitioner rely on cases cited by Petitioner's counsel at oral argument, *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373 (Fed. Cir. 2003) and *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012) (stating that, consistent with the Court's precedent, a patentability analysis considers the process in which a product is formed only where the process imparts distinctive structural characteristics). *See also Arbutus Biopharma Corp. v. Modernatx, Inc*. (Fed Cir. 2020-1183, April 11, 2023) (affirming PTAB conclusion that an ordinary artisan following the disclosures would produce a composition with the inherent morphological property based on

Petitioner's own expert confirms that the markers produced can depend on factors such as time, temperature, and cell source. *See* Ex. 1089 ¶ 27 (Dr. Olson, stating "specific growth media and culture conditions are more important for preferentially culturing cells with a particular marker pattern compared to what additional tissues are also present in the culture"). Particularly persuasive to the point that multiple factors can influence the marker expression profile is the following discussion in Rojewski:

> The differences in various surface marker expressions observed by different investigators might be due to several factors. . . Most obviously, the tissue from which MSC are derived may play an important role for surface marker expression. . . . there were variations in the percentage of positive cells after 4 passages (plastic adherence method for isolation) expressing positive markers, mainly CD73, CD105, and CD166. . . Age and sex of MSC donors may play an important role. . . .It is not clear to what extend [sic] the surface marker expression is affected by the method used for isolation of MSC. Manipulating MSC might result in up- or down-regulation of markers . . . Senescence may play an important role during expansion of MSC for clinical purposes. Mareddy et al. [5] demonstrated recently that slow growing MSC clones may show senescence and reduced differentiation capacity but still express normal levels of standard MSC surface markers like CD29, CD44, CD90, CD105, and CD166. . . . MSC phenotype might be influenced by the culture conditions for ex vivo expansion, e.g. type of supplements (fetal bovine serum, human serum, platelet lysate). . . . The use of different detection methods (flow cytometry, ELISA, micro array, reverse transcription polymerase chain reaction (RT-PCR)) and individual variations within these detection systems like antibody specificity or fluorochrome (fig. 2) may also result in differences in expression profiling.. . . All things considered,

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limited number of variable factors). Here, the structural characteristics, marker expression/non-expression, have not been shown to be present in Majore's cells.

> the known surface proteins described for the characterization of MSC are not sufficient to distinguish between subpopulations and different cell types with different intrinsic qualities of MSC. Search for surface antigens representing the pure, native MSC population within the different basic raw materials remains one of the most challenging topics of MSC research for the future. In addition, easy methods for a robust characterization of expanded MSC that do not loose pluripotency or show chromosomal abnormalities due to culturing artifacts have to be established.

Ex. 1014, 174–180, 182.

We recognize that the process steps of claim 1 are quite broad when construed in light of the patent and that the source tissue in Majore would contain subepithelial tissue. But, as the '176 patent discloses no guidance as to how such factors are to be controlled to ensure that the claimed marker expression results, we are not persuaded that an ordinarily skilled artisan practicing the method of Majore would, inevitably, as inherency requires, produce the claimed isolated cell. Although Majore cites to ISCT criteria for support as to the markers produced by MSCs, that criteria alone does not mean that all MSCs, including Majore's, necessarily satisfy those criteria. We are persuaded in this regard by Dr. Burger's testimony that Majore's isolated cell population did not differentiate under standard *in vitro* conditions despite that the ISCT criteria for MSCs require these conditions. *See* Ex. 2022 ¶ 152; Ex. 1011, 28.

We are further persuaded by Patent Owner's argument that the only testing evidence of record that confirms marker selection of isolated cells is Dr. Patel's, performed in support of his Section 1.132 declaration during prosecution. *See* Ex. 2011 ¶ 8. In that declaration, Dr. Patel presented data generated under this direction that was "introduced to show that the claimed cells have a different gene expression profile and cellular function as

compared to control cells isolated via conventional isolation techniques." *Id.* ¶ 4. Umbilical cord cells were "isolated as described in the [patent application]" with Wharton's jelly and other material removed, and the "[u]mbilical cord tissue was placed interior side down such that the subepithelial layer was in contact with the growth substrate. No enzymatic digestion was employed." *Id.* ¶ 6. The gene expression was assessed and profiled as compared to control umbilical cord cells. *Id.* ¶¶ 7, 8.

We acknowledge Petitioner's critique of this testing, that Dr. Patel's method was not a traditional explant procedure but rather a "whole umbilical cord that was digested in its entirety" and therefore not a good comparison to the disclosed methods leading to the isolated cell of claim 1. *See* Tr. 14:7–15:7. However, Dr. Patel's declaration, even if not a perfect comparison to the method of Majore, is at least some evidence that use of a different process to create an isolated cell can result in a different marker expression profile. Ex. 2011, ¶ 8.

Absent other evidence confirming identity of the limiting marker expression pattern, we are not persuaded that the resulting isolated cell necessarily has the claimed expression profile. Although the isolated cell of Majore *may* have the claimed expression profile, this is insufficient for a finding of inherency. "Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency." *Scaltech Inc. v. Retec/Tetra L.L.C.*, 178 F.3d 1378, 1384 (Fed. Cir. 1999).

b) Claims 2–13, and 15

Claims 2–13 and 15 depend from claim 1. Claims 2 and 3 recite the expression or non-expression of additional markers not tested in Majore.

Ex. 1001, 19:20–25. Claims 4–6 recite that the cells are positive for SOX2, OCT4, or both. *Id.* at 19:26–20:2. Claim 7 recites an isolated cell of claim 1 with the ability to differentiate into one of a group of specified cell types and claims 11–14 recite isolated cells of claim 1 that have differentiated into individual of the enumerated cell types. *Id.* at 20:3–7, 20:19–26. Claim 8 recites the production of specified exosomes. *Id.* at 20:8–10. Claim 9 recites culturing the cell of claim 1 in animal component-free media. *Id.* at 20:11–13. Claims 10 and 15 recite cultures of differentiated cells derived from a cell of claim 1. *Id.* at 20:14–18, 20:27–28.

For the reasons explained above, Petitioner has not shown persuasively that the cells isolated by Majore would necessarily have the expression pattern of claim 1, and thus these dependent claims are likewise not shown to be anticipated.

F. Ground 2 - Obviousness of Claim 14 over Majore and Mistry

1. Mistry (Ex. 1015)

Mistry is directed to methods for isolating cells from mammalian umbilical cord tissue that are "capable of self-renewal and expansion in culture" and "have the potential to differentiate into cells of other phenotypes." Ex. 1015, 3:17–22. Mistry teaches that culture media for cells is "known in the art for affecting differentiation of such potent cells [stem cells like MSCs] into specific types of cells or progenitors of specific cells." *Id.* at 11:34–38. Mistry discloses that a need for therapy methods to "slow the progression of and/or cure heart disease, such as ischemic heart disease and congestive heart failure" means that "[c]ells that can differentiate into cardiomyocytes that can fully integrate into the patient's cardiac muscle

without arrhythmias are highly desirable." *Id.* at 90:59–64. Mistry discloses that "umbilicus-derived cells were treated with 5-azacytidine alone or in combination with DMOS or chelerythrine chloride, and markers of cardiomyocytes measured by real-time PCR." *Id.* at 91:9–13. Mistry confirmed that the treated cells expressed markers of cardiomyocytes relative to control cells. *Id.* at 91:60–92:3.

2. Analysis

Claim 14 recites an isolated cell of claim 1 that has differentiated into a cardiomyocyte cell. Petitioner argues that a skilled artisan "would have been motivated to combine the teachings of Mistry and Majore to produce MSC cell therapies for the treatment of disease," in this case, to create a cardiomyocyte therapeutic for cardiac disease. Pet. 29 (citing Ex. 1007 ¶¶ 85, 123). Patent Owner does not address Ground 2. *See generally* PO Resp.

For the same reasons explained in II.E.2. above with respect to Ground 1, we find that Petitioner has not shown persuasively that the cells isolated by Majore would have the expression pattern of claim 1, and thus Majore and Mistry do not render claim 14 obvious.

G. Ground 3 – Obviousness of Claims 1–13, and 15 over Majore, Pierantozzi, Rojewski, Meiron, and Riekstina

1. Pierantozzi (Ex. 1012)

Pierantozzi discloses that because "MSCs from human adult tissues represent a promising source of cells for a wide range of cellular therapies, there is high interest in better understanding the mechanisms underlying proliferation, differentiation, and heterogeneity of these cells." Ex. 1012, 915. Pierantozzi examined MSCs from human bone marrow, adipose tissue,

and cardiac tissue that were isolated and cultured to 80% confluence. *Id.* at 916. Pierantozzi induced ostoeogenic and chondrogenic differentiation in the MSC populations using culture serum containing substances causing differentiation. *Id.* at 916–17. Expression of genetic markers in freshly isolated MSCs as compared to MCSs grown to 80% confluence was performed by reverse transcriptase-PCR to amplify extracted RNA, immunofluorescence, and immunoprecipitation assays. *Id.* at 917–18. Pierantozzi discloses that "NANOG was not expressed in freshly isolated MSCs, but was detected only after in vitro culture. NANOG was detected only in proliferating cells, but not in MSCs induced to differentiate." *Id.* at Abstract. Pierantozzi states "we propose that activation of NANOG expression in MSCs is associated with, although cannot directly regulate, the transition from in vivo quiescence to adaptation to in vitro growth conditions." *Id.*

2. Rojewski (Ex. 1014)

Rojewski discloses that MSCs are "candidates for several clinical applications" to treat injury and disease and that because "MSC isolated from different tissues do not represent a homogenous cell population," it is necessary to characterize and perform quality control to understand the variations. Ex. 1014, 168, 173. Rojewski conducted a review to "summarize various different attempts to characterize mesenchymal stem cells based on surface protein expression by flow cytometry and to define multipotent subpopulations of mesenchymal stem cells for prospective isolation." *Id.* at 168 (Summary). Rojewski discloses a summary of phenotype data of the reviewed MSCs isolated from various tissues and

provides a summary of data regarding expression of genetic markers. *Id.* at 169–173 (Table 1).

3. Meiron (Ex. 1016)

Merion is directed to "methods of treating diseases using adherent cells [MSCs] from adipose or placenta tissues, more specifically, to methods of treating ischemia and/or medical conditions requiring connective tissue regeneration and/or repair using the adherent cells." Ex. 1016, 1:6–9. Meiron discloses:

> In recent years, considerable activity has focused on the therapeutic potential of mesenchymal stromal cells (MSCs) for various medical applications including tissue repair of damaged organs such as the brain, heart, bone and liver and in support of bone marrow transplantations (BMT). MSCs, a heterogeneous population of cells obtained from e.g. bone marrow, adipose tissue, placenta, and blood, is capable of differentiating into different types of mesenchymal mature cells (e.g. reticular endothelial cells, fibroblasts, adipocytes, osteogenic precursor cells) depending upon influences from various bioactive factors.

Id. at 1:16–23.

Meiron analyzed the expression markers for its cells and discloses:

> stromal stem cell surface markers (positive and negative) include but are not limited to CD105+, CD29+, CD44+, CD73+, CD90+, CD3-, CD4-, CD34-, CD45-, CD80-, CD19-, CD5-, CD20-, CD11B-, CD14-, CD19-, CD79-, FILA-DR-, and FMC7-. Other stromal stem cell markers include but are not limited to tyrosine hydroxylase, nestin and H-NF.

Id. at 20:23–28.

4. Riekstina (Ex. 1013)

Riekstina discloses a study of stem cell marker expression patterns in MSCs isolated from human bone marrow, adipose tissue, heart tissue, and dermal tissue. Ex. 1013, 378–79. Riekstina discloses that the

"immunomodulatory and regenerative potential" of MSCs has shown "promising results in preclinical and clinical studies for a variety of conditions, such as graft versus host disease (GvHD), Crohn's disease, osteogenesis imperfecta, cartilage damage and myocardial infarction." *Id.* Riekstina discloses:

> Our findings provide evidence that bone marrow MSCs express embryonic stem cell markers Oct4, Nanog, alkaline phosphatase and SSEA-4, adipose tissue and dermis MSCs express Oct4, Nanog, SOX2, alkaline phosphatase and SSEA-4, whereas heart MSCs express Oct4, Nanog, SOX2 and SSEA-4. Our results also indicate that human adult mesenchymal stem cells preserve tissue-specific differences under in vitro culture conditions during early passages, as shown by distinct germ layer and embryonic stem cell marker expression patterns.

Id. at 385.

5. Analysis

Petitioner argues, through Dr. Olson, that a skilled artisan would have understood that the teachings of references related to umbilical cord MSCs are relevant to teachings directed to MSCs derived from other tissues. Pet. 30–31 (citing Ex. 1007 ¶ 127). In addition, Petitioner argues that the skilled artisan would have understood from the teachings of Pierantozzi and Majore that MSCs derived from various tissues could be useful alternatives (e.g., are interchangeable). *Id.* Petitioner argues that a skilled artisan would have had an expectation of success in combining the teachings of Majore with Pierantozzi, Rojewski, Merion, and Reikstina to arrive at the subject matter of the Challenged Claims because "it would be completely unsurprising and, indeed, predictable for Majore's MSCs to express markers previously observed as expressed on MSCs in the prior art." *Id.* at 32 (citing Ex. 1007 ¶ 86). According to Petitioner, "a POSITA [person of ordinary skill in the

art] would understand that expression patterns of MSCs from any tissue are informative of the biological properties of MSCs generally, and that MSCs from various tissues can often be used interchangeably for the proposed mechanisms of most cell therapies." *Id.* For this reason, Petitioner argues, a skilled artisan would have been motivated to combine the cited prior art "for the purpose of improving MSC cellular therapies." *Id.* at 32–33 (citing Ex. 1007 ¶¶ 86, 127–131).

a) Claim 1

Specific to claim 1, Petitioner argues that "Majore also renders 1[Pre], 1[A], 1[B], and 1[C] obvious because Majore discloses isolating cells from whole umbilical cord using an explant procedure." Pet. 33 (citing Ex. 1007 ¶ 132). Petitioner argues that "a POSITA would have been able to predict that an isolated cell can be prepared by placing a subepithelial layer of mammalian umbilical cord tissue in direct contact with a substrate, and culturing the subepithelial layer such that the isolated cell is capable of self-renewal and culture expansion." *Id.* (citing Ex. 1007 ¶ 132).

Petitioner argues that Rojewski and Merion teach limitations [C] and [D], and Pierantozzi discloses "the non-expression of NANOG in some fraction, or all, of the MSCs freshly isolated from adult tissues." *Id.* at 34–35 (citing Ex. 1007 ¶ 136). Petitioner contends that "a POSITA would understand the detection of NANOG expression is exquisitely sensitive to the conditions used to culture the cells and the details of the detection method used." *Id.* Petitioner further argues that the skilled artisan would have known that the isolated cells of Majore would include MSCs having identical genetic marker expression profiles to the cells of the Challenged Claims based on the ISCT criteria and the teachings of, Rowjewski, Merion,

and Pierantozzi, rendering claim 1 obvious. *Id.* at 33–35 (citing Ex. 1007 ¶¶ 99, 133–139).

As we concluded in Section II.E.2.a above that Majore discloses limitations Pre[A], [B], and [D], we summarize Patent Owner's arguments only relating to whether Majore, Pierantozzi, Rojewski, Meiron, and Riekstina disclose limitations [C] and [E], and regarding the skilled artisan's motivation to combine and reasonable expectation of success.

Patent Owner raises the same arguments against Majore's teaching of limitations [C] and [E] discussed above. PO Resp. 37–38. Patent Owner argues that the isolated cell is "solely from the subepithelial layer" and that the ordinary artisan would not have had reason to isolate the cells from that tissue. *Id.* at 35. Patent Owner argues that, even with the combination of references, not all claim limitations are taught. *Id.* at 36. Patent Owner argues that obviousness cannot be supplied through predictions or general guidance. *Id.* (citing *Teva Pharms, USA, Inc. v. Sandoz Inc.*, 906 F.3d 1013, 1025 (Fed. Cir. 2018), *In re Stepan Co.*, 868 F.3d 1342, 1347 (Fed. Cir. 2017)).

Patent Owner notes that Majore is silent as to NANOG and argues that Pierantozzi "teaches away from NANOG- negative cultured cells" because Pierantozzi discloses NANOG was "expressed in freshly isolated MSCs detected after *in vitro* culture," which is when the Challenged Claims recite NANOG should not be expressed. *Id.* at 36–37. Patent Owner argues that Petitioner cites "Pierantozzi's *pre-culture* detection of NANOG," noting "[t]he claimed cells recite positive NANOG expression after culturing, not before." *Id.* at 37 (citing Ex. 2022 ¶ 178).

Patent Owner argues that Rojewski does not identify "any *particular* MSC populations that include *all* the markers asserted by Petitioner" and that Petitioner does not allege that Rojewski teaches cells including all recited marker or even that Rojewski teaches cells derived from the subepithelial layer of umbilical cord tissue. *Id.* at 38. Patent Owner argues that there is no reason to believe that the ordinary artisan would have believed a marker produced in, e.g., bone marrow would also be produced in an MSC from subepithelial tissue, particularly in light of Rojewski's disclosures that marker expression varies between tissue types, along with conflicting marker tissue expression levels from various MSCs isolated from different tissues. *Id.* at 38–39 (citing Ex. 2022 ¶¶ 123–126). Patent Owner notes that Rojewski reports "at least four [markers] (i.e., CD45, CD34, CD14, CD117)" that do not meet claim 1's requirement of non-expression. *Id.* at 40.

Patent Owner argues Meiron's teaching of genetic markers in stromal cells "does not disclose a cell population with the recited marker expression/non-expression" and would not give a skilled artisan a basis to believe that the claimed markers would be expressed in Majore's cells. *Id.* at 40–41 (citing Ex. 2022 ¶ 194).

Upon consideration of the arguments and evidence, we find that Petitioner has not shown sufficiently that Majore alone teaches limitation [C] or [E] for the reasons discussed above in Ground 1. With regard to Petitioner's arguments that the ordinary artisan would have been able to predict that an isolated cell having the recited marker profile could be made by placing a subepithelial layer of mammalian umbilical cord tissue in direct contact with a substrate, and culturing to self-renewal, we find that Petitioner

has not provided sufficient evidence to support this assertion. Petitioner cites Dr. Olson's testimony as the sole support for this assertion. Dr. Olson's testimony is a close restatement of Petitioner's contentions:

> Majore renders . . . 1[C] obvious. This is so because Majore discloses isolating cells from whole umbilical cord using an explant procedure. At the priority date of the '176 patent, a POSITA would have known that MSCs were present in all umbilical cord tissues, including the subepithelial layer, and that such cells could be culture [sic] and were capable of self-renewal and culture expansion when obtained from an explant. Thus, a POSITA would have been able to predict that an isolated cell can be prepared by placing a subepithelial layer of mammalian umbilical cord tissue in direct contact with a substrate, and culturing the subepithelial layer such that the isolated cells is [sic] capable of self-renewal and culture expansion. Moreover, a POSITA would know that the isolated cells would include MSCs having the characteristics consistent with the ISCT criteria. Thus Majore renders . . . 1[C] obvious.

Ex. 1007 ¶¶ 132, 133. Importantly, however, Dr. Olson does not cite anything to support his opinion that the ordinary artisan would have known that MSCs could be cultured to be renewable from subepithelial UC tissue. Nor does Dr. Olson explain why the artisan would have had this understanding aside from simply stating it. Majore uses the word "subepithelial" only once to explain that primitive stem cells are "distributed in subepithelial and intervascular regions," but this does not teach what Dr. Olson asserts. Accordingly, Dr. Olson's testimony is entitled to little weight. *Xerox Corp.*, IPR2022-00624, Paper 9 at 15–16 (finding that an expert's conclusory assertions that repeat the proposition for which they are offered without "any additional supporting evidence or provide any technical reasoning" in support are "conclusory and unsupported, add[] little to the conclusory assertion[s] for which [they are] offered to support, and is

entitled to little weight"); *see also* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."); *Upjohn Co.*, 225 F.3d at 1311 ("Lack of factual support for expert opinion going to factual determinations, however, may render the testimony of little probative value in a validity determination.") (quoting *Ashland Oil*, 776 F.2d at 294). For this reason, we conclude that Majore does not render limitation [C] obvious.

We are likewise not persuaded that Pierantozzi, Rojewski, Meiron, or Riekstina address the deficiencies in Petitioner's allegations regarding Majore's disclosures, or that they teach limitation [E]. While we agree that an ordinary artisan would have believed that the art related to MSCs from other tissue sources and cultured in different conditions would be relevant for its teachings and *potentially* applicable to all MSCs, on the record before us, Petitioner has not shown the teachings are interchangeable. Rather, the evidence of record, including Dr. Olson's own testimony, shows that multiple conditions can affect marker expression. *See* Ex. 1089 ¶ 27, Ex. 1014, 175–180, 182. Rojewski in particular acknowledges the unpredictability in MSC marker expression. Ex. 1014, 175–180, 182. Given this unpredictability, we are not persuaded that the ordinary artisan would have reasonably believed that the teachings from Pierantozzi, Rojewski, Meiron, or Riekstina would accurately predict that Majore's MSCs would express the markers observed as expressed or discussed in those references. For instance, we are persuaded that MSCs isolated from newly-cultured cells obtained from non-umbilical cord tissue as in Pierantozzi would not reliably predict the expression pattern of established cultured umbilical cord-derived subepithelial cells due to the difference in

tissue types and age of the tissue donor. *See* PO Resp. 37 (citing Ex. 2022 ¶ 178).

For the reasons above, we find that Petitioner has not established that the ordinary artisan would have found it obvious to combine the teachings of the asserted art or would have had a reasonable expectation of success in doing so.

b) Claims 2–13, and 15

Claims 2–13 and 15 depend from claim 1. Claims 2 and 3 recite the expression or non-expression of additional markers not tested in Majore. Ex. 1001, 19:20–25. Claims 4–6 recite that the cells are positive for SOX2, OCT4, or both. *Id.* at 19:26–20:2. Claim 7 recites an isolated cell of claim 1 with the ability to differentiate into one of a group of specified cell types and claims 11–14 recite isolated cells of claim 1 that have differentiated into individual of the enumerated cell types. *Id.* at 20:3–7, 20:19–26. Claim 8 recites the production of specified exosomes. *Id.* at 20:8–10. Claim 9 recites culturing the cell of claim 1 in animal component-free media. *Id.* at 20:11–13. Claims 10 and 15 recite cultures of differentiated cells derived from a cell of claim 1. *Id.* at 20:14–18, 20:27–28.

Petitioner's allegations regarding claims 2–13 and 15 rely on its allegations asserted for claim 1. Pet. 35–39. For the reasons explained above, Petitioner has not shown persuasively that the cells isolated by Majore would have the expression pattern of claim 1, or that Pierantozzi, Rojewski, Meiron, or Riekstina cure the deficiencies in Petitioner's allegations regarding Majore's teachings. We find that Petitioner has not shown persuasively that the ordinary artisan would have found the subject

matter of claims 2–13 and 15 obvious or that the artisan would have had a reasonable expectation of success in combining the teachings to arrive at the subject matter of claims 2–13 and 15.

H. Ground 4 – Obviousness of Claim 14 over Majore, Pierantozzi, Rojewski, Meiron, and Mistry

Claim 14 recites an isolated cell of claim 1 that has differentiated into a cardiomyocyte cell. Petitioner incorporates its allegations of the teachings of the references from Ground 3. Pet. 40. Petitioner argues that Mistry teaches its "umbilical cord derived MSCs 'are capable of self-renewal and expansion in culture and have the potential to differentiate into cells of other phenotypes; for example cardiomyocytes, or their progenitors' (Mistry 18:9–13) via treatment with 5-azacytidine (Mistry at 90:56–91:30)." *Id.* (citing Ex. 1007 ¶ 166). Petitioner relies on its earlier arguments regarding the teachings of Majore, Pierantozzi, Rojewski, Merion, and Mistry to contend they render claim 14 obvious. *Id.*

Petitioner argues that a skilled artisan "would be motivated to combine the teachings of Majore, Pierantozzi, Rowjewski, Merion, and Mistry for the purpose of improving cellular therapies using MSCs because each reference discloses the potential therapeutic applications of MSCs." *Id.* (citing Ex. 1007 ¶ 165). Petitioner argues the artisan would have also had an expectation of success in making the claimed subject matter. *Id.* (citing Ex. 1007 ¶ 87).

Patent Owner makes no arguments regarding Ground 4. *See generally* PO Resp.

For the same reasons explained in II.G.5. above with respect to Ground 3, we find that Petitioner has not shown persuasively that the

ordinary artisan would have found the subject matter of claims 14 obvious or that the artisan would have had an expectation of success in combining the teachings to arrive at the subject matter of claim 14.

I. Ground 5 – Obviousness of Claims 1–15 over Phan, Pierantozzi, Rojewski, Meiron, and Riekstina

1. Phan (Ex. 1017)

Phan discloses a method for isolating "stem/progenitor cells from the amniotic membrane of umbilical cord" comprising "separating the amniotic membrane from the other components of the umbilical cord *in vitro*, culturing the amniotic membrane tissue under conditions allowing cell proliferation, and isolating the stem/progenitor cells from the tissue cultures." Ex. 1017 ¶ 1. Phan discloses that its method includes "separating the cells from the amniotic membrane tissue before cultivation by a technique selected from the group consisting of enzymatic digestion and direct tissue explant." *Id.* ¶ 10. Phan explains that the "term 'direct tissue explant technique' as used herein means that the tissue is first placed in media without enzymes. Then the cells separate from the main tissue mass and are harvested for collection." *Id.* ¶ 40. Phan discloses an embodiment in which the method is used to isolate "epithelial and/or mesenchymal stem/progenitor cells." *Id.* ¶ 43. The cells are cultured under "conditions allowing the cells to undergo clonal expansion." *Id.* ¶ 13. The cells "can ultimately be differentiated into, but not limited to, by morphology, epithelial or mesenchymal cells" which can include "skin fibroblasts, chondrocytes, osteoblasts, tenocytes, ligament fibroblasts, cardiomyocytes, smooth muscle cells, skeletal muscle cells, adipocytes, cells derived from endocrine glands, and all varieties and derivatives of neurectodermal cells."

Id. ¶¶ 42, 45. The cells "expressed 140 genes related to embryonic stem cells and embryonic development . . . [including] Nanog." *Id.* ¶ 88.

2. Analysis

a) Claim 1

Petitioner argues that the combination of Phan, Pierantozzi, Rojewski, Meiron, and Riekstina teaches all limitations of claim 1, and that the ordinary artisan would have been motivated to combine their teachings to make the claimed cell. Pet. 41–48. Petitioner argues that the method of Phan produces the claimed cell. *Id.* at 41. Patent Owner disagrees. PO Resp. 48–55.

We evaluate whether the evidence of record shows, by a preponderance of the evidence, that the process of Phan would have resulted in an "an isolated cell" having the marker characteristics of limitations [C], [D], and [E] recited in claim 1, despite any differences between Phan's process and the process limitations of claim 1, i.e., limitations [A] and [B].

(1) ([Preamble] and [A]) "An isolated cell prepared by a process comprising placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate

(2) ([B]) culturing the subepithelial layer such that the isolated cell from the subepithelial layer is capable of self-renewal and culture expansion

Petitioner argues that Phan discloses [Pre], [A], and [B] "including the process of contacting the amniotic membrane of umbilical cord with a growth substrate and culturing the tissue such that the isolated cells are capable of self-renewal and culture expansion." Pet. 41–44 (citing Ex. 1007 ¶¶ 167, 169–172). Petitioner argues that "the umbilical cord tissue termed 'amniotic membrane' in Phan is the **same tissue** as the 'subepithelial layer' as disclosed in the '176 patent." *Id.*; *see also* Pet. Reply 19–20, arguing that

Patent Owner's experts' distinctions as to the types of membranes are misleading and that Phan cultures epithelial cells, not MSCs. Petitioner argues that Phan discloses the use of stem cell therapies for treating human and animal disease. Pet. 41.

Patent Owner argues that Phan does not culture the subepithelial cell layer, but rather "discloses cutting up the amniotic membrane and placing it on culture dishes." PO Resp. 48. Patent Owner additionally argues that Phan discloses culturing amniotic membrane cells using collagenase treatment, but that the method used was not a cell growth medium, meaning Phan could not have performed the step of culturing the subepithelial layer. *Id.* at 49–51.

Patent Owner argues that Phan does not disclose using the subamniotic membrane and that Petitioner's efforts to show how Phan's disclosure results in culture of the subamniotic membrane fail. PO Resp. 48–51 (citing Ex. 2022 ¶¶ 235–248). Patent Owner argues that Phan does not mention "subamniotic membrane" in its disclosure and that the portion Petitioner identifies to be amniotic membrane is mis-identified. *Id.* at 48–50. Patent Owner argues the ordinary artisan would have understood that "any stem cells capable of self-renewal, also had positive NANOG expression, 'one of the key molecules necessary for the maintenance of self-renewal of SCs.'" *Id.* at 51 (citing Ex. 1010, 494–95; Ex. 2022 ¶ 298; Ex. 2027 ¶¶ 23–26). Patent Owner argues that the ordinary artisan would not have predicted that the claimed cells were capable of renewal because they do not express NANOG, while Phan does. *Id.* Patent Owner also argues that Petitioner did not test Phan's methods to confirm that positive

NANOG expression occurred, preferring to rely on expected results.

PO Sur-Reply, 5–6.

As discussed in Section II.D. regarding claim interpretation, we do not construe "placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate" to require placing the subepithelial layer interior side down in direct contact with the substrate. Both Phan and the '176 patent disclose using explant methods to foster cell culture and replication from tissue harvested from umbilical cord. *See* Ex. 1017 ¶¶ 1, 41, 42, 45, 88; Ex. 1001, 13:57–14:5. Both methods result in adherent subepithelial cells growing on a plastic growth surface awash in culture media. *Id.* Thus, we find Petitioner has established by a preponderance of evidence that Majore teaches the preamble and limitations [A] and [B].

(a) ([D]) wherein the isolated cell expresses at least three cell markers selected from the group consisting of CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, or CD105

([C] and [E]) wherein the isolated cell does not express NANOG and at least five cell markers selected from the group consisting of CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR

Petitioner argues that Pierantozzi, Rojewski, Merion, and Riekstina teach [C] and [D][23]. Pet. 46–48. Petitioner relies on its earlier characterizations of the teachings of Pierantozzi, Rojewski, Merion, and Riekstina as described above regarding "MSCs from various tissues [that]

[23] In its Ground 5 analysis, Petitioner conflates limitation [D] (at least three cell markers expressed) with [C] and limitation [E] (at least five markers not expressed] with [D], and addresses all three limitations together. *See* Pet. 45–48. For the sake of completeness, we analyze each of [C], [D], and [E] as if they had been correctly addressed.

are known to express (or not express) the markers recited in the '176 patent claims." *Id.* at 41.

With regard to NANOG expression, Petitioner argues that while "Phan discloses NANOG expression was detected in a global gene expression microarray of isolated MSCs," Pierantozzi discloses that newly isolated MSCs do not express NANOG, and that later expression suggests an adaptation of these cells as they adapt to *in vitro* culture conditions. *Id.* at 47 (citing Pierantozzi). Petitioner argues that the ordinary artisan would understand that the freshly isolated cells of Phan do not express NANOG, notwithstanding Phan's characterization of older, tissue culture-adapted MSCs. *Id.* (citing Ex. 1007 ¶¶ 175–178).

Petitioner argues that because the cited art is directed to use of MSCs to treat disease, a skilled artisan "would have been motivated to consult each of Pierantozzi, Rojewski, Merion and Riekstina to fill in any gaps with respect to the marker or differentiation potential of the MSCs made using the Phan methodology." *Id.* at 42. Petitioner further argues that a skilled artisan would have had an expectation of success as it would have been "completely unsurprising and predictable for Phan's MSCs to express markers" previously reported in the prior art as expressed by MSCs. *Id.* Petitioner alleges the skilled artisan would have believed the "expression patterns of MSCs from any tissue are informative of the biological properties of MSCs generally, and MSCs from various tissues can often be used interchangeably in cell therapies," and thus the skilled artisan would have been motivated to combine the art for the purpose of improving cellular therapies. *Id.* (citing Ex. 1007 ¶¶ 88, 168).

Patent Owner argues none of [C], [D], or [E] is disclosed. PO Resp. 52–55. Patent Owner argues through Dr. Olson that "Phan cultured tissues from both the epithelium and subepithelium, not solely from the subepithelial layer," which would result in cells with a different gene marker profile than the claimed cell. *Id.* (citing Ex. 2027 ¶ 33).

Patent Owner argues that Phan notes that NANOG expression is related to embryonic stem cell development and Pierantozzi discloses positive NANOG expression for cultured cells. *Id.* at 52. Patent Owner argues that Dr. Olson's testimony that MSCs with different lineage commitment may result in varied expression of NANOG is inconsistent with record evidence and that no record evidence supports the requirement of the claimed cells to be NANOG negative. Rather, Patent Owner argues, "the POSITA would believe positive NANOG expression in cultured cells was a defining characteristic of MSCs." *Id.* (citing Ex. 2027 ¶¶ 23–24). Patent Owner incorporates its prior arguments related to the remaining references. *Id.* at 53–55.

Upon analysis of the full record, including the parties' arguments and evidence, Petitioner has not shown persuasively that the alleged combination of references teaches limitations [C], [D], or [E].

In light of our claim interpretations explained above, we find that Phan discloses a method of producing an isolated cell by placing mammalian umbilical cord tissue in direct contact with a growth substrate and culturing those cells to create a stable cell line capable of self-renewal and culture expansion. Ex. 1017 ¶¶ 1, 9, 13, 40, 42, 44. However, Phan's process differs from at least the interior-down embodiment disclosed in the '176 patent, which Patent Owner claims is the focus of the claims at issue. PO

Sur-Reply 19. The '176 patent Specification does not disclose whether *every* disclosed embodiment or the broad process parameters disclosed therein would necessarily result in a marker profile consistent with claim 1. *See* Ex. 1001, 8:6–12; 8:29–31 (providing various marker expression profiles for disclosed aspects of cells). Indeed, as noted above, the claim language itself recognizes that cells prepared according to the process limitations of limitations [A] and [B] would not all have the exact same marker expression profile. As a result, Petitioner's reliance on Phan's process to prove the identity of Phan's cells to the claimed cell does not *necessarily* establish production of the marker profile even though Phan may satisfy the process limitations as we have construed them.

With regard to Petitioner's arguments that the ordinary artisan would have been able to predict that an isolated cell having the recited marker profile could be made by placing a subepithelial layer of mammalian umbilical cord tissue in direct contact with a substrate and culturing to self-renewal, we find Petitioner has not provided sufficient evidence to support this assertion. Petitioner cites Dr. Olson's testimony as the sole support for this assertion. Pet. 41–44 (citing Ex. 1007 ¶¶ 167, 169–172). Dr. Olson does not cite anything to support his opinion that the ordinary artisan would have known that MSCs could be cultured to be renewable from subepithelial UC tissue. Rather Dr. Olson's testimony is grounded in inherency:

> Importantly, the umbilical cord tissue termed "amniotic membrane" in Phan is the same tissue as the "subepithelial layer" as disclosed in the '176 patent. *See, e.g.*, Phan, Fig. 16. Thus, the cells produced by the process of the '176 patent are also produced by the process disclosed by Phan.

Ex. 1007 ¶ 167. Yet, Dr. Olson's testimony does not meet the standard for inherency. *See, e.g.*, *Scaltech*, 178 F.3d at 1384 ("Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency."). Nor does Dr. Olson explain why the artisan would have had this understanding aside from simply stating it. We accord such testimony little weight. *See Xerox Corp.*, IPR2022-00624, Paper 9 at 15–16; 37 C.F.R. § 42.65(a); *Upjohn*, 225 F.3d at 1311.

Even assuming we agreed with Dr. Olson's conclusion, which we do not, Petitioner has not provided any evidence that the marker expression profile is *only* dependent on the process used to produce the claimed cells while the evidence of record shows that multiple factors can influence the marker expression profile. *See supra* II.E.2. We are not persuaded that an ordinarily skilled artisan practicing the method of Phan would, without fail, as inherency requires, produce the claimed isolated cell. *See also* Ex. 2022 ¶¶ 259, 260 (Dr. Burger testimony regarding differences in gene expression between Phan's cells and claimed cell).

Turning to Petitioner's allegations of obviousness, Petitioner does not sufficiently explain why the ordinary artisan would have been motivated to combine the teachings of the asserted references to obtain the claimed subject matter. Dr. Olson's rationale for the combination is stated below:

> Although Phan does not expressly disclose the markers recited in the '176 patent claims, Pierantozzi, Rojewski, and Merion disclose that MSCs from various tissues are known to express (or not express) the markers recited in the '176 patent claims. Furthermore, similar to Pierantozzi, Rojewski, and Merion, Phan discloses that "[s]tem cell-based therapies thus have the potential to be useful for the treatment of a multitude of human and animal disease." Phan, pgs 1-2. Thus, a person of ordinary

> skill in the art would be motivated to combine the teachings of Phan with Pierantozzi, Rojewski, and Merion for the purpose of improving cellular therapies employing MSCs.

Ex. 1007 ¶ 168 (alteration in original). We agree that an ordinary artisan would be motivated to look to the teachings of analogous references for information, but to establish obviousness, a party must show that "there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (requiring "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness")). Petitioner has not provided sufficient rationale to explain why the ordinary artisan would have been motivated to make the isolated cell with the specific marker profile or why the artisan would have looked to the cited references themselves out of the wide range of references available in the art.

We are likewise not persuaded that Pierantozzi, Rojewski, Meiron, or Riekstina address the deficiencies in Phan, or that they teach limitation [E]. While we agree that an ordinary artisan would have believed that the art related to MSCs from other tissue sources and cultured in different conditions would be relevant for its teachings and *potentially* applicable to all MSCs, on the record before us, that Petitioner has not shown the teachings are interchangeable. Rather, the evidence of record, including Dr. Olson's own testimony, shows that multiple conditions can affect marker expression. *See* Ex. 1089 ¶ 27; Ex. 1014, 175–180, 182. Rojewski in particular acknowledges the unpredictability in MSC marker expression. Ex. 1014, 175–180, 182. Given this unpredictability, we are not persuaded that the ordinary artisan would have reasonably believed that the teachings from Pierantozzi, Rojewski, Meiron, or Riekstina would accurately predict

that Phan's MSCs would express the markers observed as expressed or discussed in those references. For instance, we are persuaded that MSCs isolated from newly-cultured cells obtained from non-umbilical cord tissue as in Pierantozzi would not reliably predict the expression pattern of established cultured umbilical cord-derived subepithelial cells.

For the reasons above, we find that Petitioner has not established that the ordinary artisan would have found it obvious to combine the asserted art or would have had a reasonable expectation of success in making the subject matter of claim 1 by combining the teachings.

b) Claims 2–15

Petitioner's allegations regarding claims 2–15 rely on its allegations asserted for claim 1. Pet. 48–53. For the reasons explained above, Petitioner has not shown persuasively that the cells isolated by Phan would have the expression pattern of claim 1, or that Pierantozzi, Rojewski, Meiron, or Riekstina cure the deficiencies in Petitioner's allegations regarding Phan's teachings. In addition, for the reasons we address above regarding the incompatibility of teachings from the references, we find that Petitioner has not shown persuasively that the ordinary artisan would have found the subject matter of claims 2–15 obvious or that the artisan would have had an expectation of success in combining the teachings to arrive at the subject matter of claims 2–15.

J. Ground 6 – Obviousness of Claims 1–8, 10–13, and 15 by Kita, Pierantozzi, Rojewski, Meiron, and Riekstina

1. Kita (Ex. 1010)

Kita discloses a protocol to "isolate adult SCs from the cord lining membrane (subamniotic region of the umbilical cord), and characterize the

isolated cells as a novel source for cell-based therapeutic approaches." Ex. 1010, 492. Human umbilical cord was obtained, washed, and cut into 1-inch pieces and dissected to open the cord, then placed in petri dishes with growth medium and incubated. *Id.* Wharton's jelly inside the cord was dissected away, and pieces of "outer envelope membranes" were cultured in growth medium. *Id.*

Figure 1 C, reproduced below, shows the location of the subamnion cells dissected out for study:

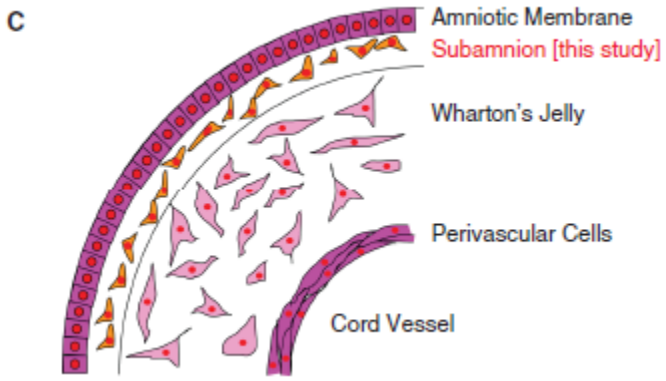

Figure 1 C is a "[d]iagram of the origin of cord lining membrane (CL)-mesenchymal stem cells (MSCs)." *Id.* at 493.

Kita discloses:

> Approximately 10 to 14 days after starting the culture, a significant number of cells migrated from the implants into the petri dishes. Morphologically, most of cells appeared to be fibroblastoid (Fig. 1B, left), but we could also see a small population of epithelial-like cells when amniotic membrane was used as a source.

Id. at 494. Kita states that the minor population of epithelial-like cells were believed to be "subamnion region-derived cells." *Id.* at 493 (Fig. 1 legend). Osteogenic and adipogenic differentiation were successfully induced in the cell populations. *Id.* at 492.

2. Analysis

Petitioner argues that the combination of Kita, Pierantozzi, Rojewski, Meiron, and Riekstina teaches all limitations of the Challenged Claims, and that the ordinary artisan would have been motivated to combine their teachings to make the claimed cell. Pet. 53–66. Patent Owner disagrees. PO Resp. 59–65.

We evaluate whether the evidence of record shows, by a preponderance of the evidence, that the process of Kita would have resulted in an "an isolated cell" having the marker characteristics of limitations [C], [D], and [E] recited in claim 1, despite any differences between Kita's process and the process limitations of claim 1, i.e., limitations [A] and [B].

a) Claim 1

(1) ([Preamble] and [A]) "An isolated cell prepared by a process comprising placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate

([B]) culturing the subepithelial layer such that the isolated cell from the subepithelial layer is capable of self-renewal and culture expansion

Petitioner claims Kita teaches [Pre], [A], and [B] of claim 1 of the '176 patent by isolating MSCs from umbilical cord, placing pieces of the separated subamniotic membrane onto the surface of a tissue culture substrate, and culturing them. Pet. 55–57 (citing Ex. 1007 ¶¶ 203–207). Petitioner argues that a skilled artisan would have recognized Kita's teachings to include the steps of [Pre], [A], and [B]. *Id.* at 57 (citing Ex. 1007 ¶ 208).

Patent Owner argues that Kita's method includes more than subepithelial tissue and that the ordinary artisan would understand this.

PO Resp. 59. Patent Owner argues that "different starting points in tissue culture yields different marker expression profiles." *Id.*

As discussed in Section II.D regarding claim interpretation, we do not construe "placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate" to require placing the subepithelial layer interior side down in direct contact with the substrate. Both Kita and the '176 patent disclose using methods to foster cell culture and replication from tissue harvested from umbilical cord. *See* Ex. 1010, 492, Fig. 1C; Ex. 1001, 2:9–20. Both methods result in adherent subepithelial cells growing on a plastic growth surface awash in culture media. *See* Ex. 1010, 492, Fig. 1C; Ex. 1001, 2:9–20. Thus, we find Petitioner has established by a preponderance of evidence that Majore teaches the preamble and limitations [A] and [B].

(2) ([D]) wherein the isolated cell expresses at least three cell markers selected from the group consisting of CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, or CD105

Petitioner alleges that step [D] of claim 1 has no patentable weight, or, in the alternative, that Kita discloses that "MSCs isolated from the subamnion express each of CD29, CD73, CD90, SSEA4, CD44, CD146 and CD105." Pet. 57–58 (citing Ex. 1007 ¶ 209, Table 3). Petitioner also alleges that Rojewski and Merion disclose the "at least three" markers recited in [C][24]. *Id.* (citing Ex. 1007 ¶¶ 209, 210).

[24] In its Ground 6 analysis, Petitioner conflates limitation [D] (at least three cell markers expressed) with [C] and limitation [E] (at least five markers not expressed] with [D], and addresses all three limitations together. *See* Pet. 57–61. For the sake of completeness, we analyze each of [C], [D], and [E] as if it they been correctly addressed.

Kita discloses that its mesenchymal cells expressed at least five of the recited cell markers. Ex. 1010, 495. We find that Petitioner has established by a preponderance of evidence that Kita teaches limitation [D].

(3) ([C] and [E]) wherein the isolated cell does not express NANOG and at least five cell markers selected from the group consisting of CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR

Petitioner alleges that Kita discloses "MSCs isolated from the subamnion do not express CD45, CD34, and Stro-1." Pet. 59 (citing Ex. 1007 ¶ 209, Table 3). Petitioner alleges that Pierantozzi, Rojewski, and Meiron each teach non-expression of markers disclosed in [D]. *Id.* (citing Ex. 1007 ¶¶ 209, 211, Table 3).

Petitioner alleges that although "Kita discloses NANOG expression was detected by immunofluorescence and RT-PCR, it provides no data on the relative frequency of NANOG expressing cells," which were cultured. *Id.* (citing Ex. 1007 ¶ 212). Petitioner alleges that a skilled artisan would have understood that "the freshly isolated cells of Kita do not express NANOG, notwithstanding Kita's characterization of older, tissue culture-adapted MSCs" because freshly isolated MSCs do not express NANOG, as Pierantozzi teaches. *Id.* at 60 (citing Ex. 1007 ¶ 213).

Patent Owner argues Kita does not teach limitation [C] because Kita's cells fully express NANOG. PO Resp. 60. Patent Owner argues that Kita's method does not fully isolate the subepithelial tissue and that "the differences in gene marker expression are explained by the differences between Kita's tissues and protocol and the '176 Patent." *Id.*

Patent Owner argues Kita does not teach limitation [E] because Kita does not disclose that its cells did not express the requisite five markers. *Id.*

at 61. Patent Owner argues the differences in Kita's methods account for the difference in cell marker expression. *Id.* (citing Ex. 2027 ¶ 32).

Upon analysis of the full record, including the parties' arguments and evidence, Petitioner has not shown persuasively that the alleged combination of references teaches limitations [C] or [E]. Our reasoning mirrors our analysis for Grounds 3 and 5. *See* Sections II.G.1 and II.I.1. Briefly, Petitioner has not shown sufficiently that Kita's process would necessarily cause production of the recited marker profile. While Kita's cells are closer in that they satisfy limitation [D], they strongly express NANOG and Kita does not disclose non-expression of at least 5 of the markers in limitation [E]. Petitioner has not provided any evidence that the marker expression profile is *only* dependent on the process used to produce the claimed cells while the evidence of record shows that multiple factors can influence the marker expression profile. *See supra,* Section II.E.2.

Petitioner's reliance on Dr. Olson's testimony (Ex. 1007 ¶¶ 211, 212) is insufficient to close the gap as it does not provide a sufficient basis for the ordinary artisan to have been motivated to combine the teachings of the asserted references to obtain the claimed subject matter. Dr. Olson's rationale for the combination is stated below:

> Although Kita does not expressly disclose all the markers recited in the '176 patent claims, Pierantozzi, Rojewski, Merion, and Riekstina disclose that MSCs from various tissues are known to express (or not express) the markers recited in the '176 patent claims. Furthermore, similar to Pierantozzi, Rojewski, Merion, and Riekstina, Kita discloses that the use of its cells obtained from the amniotic membrane "is a promising novel approach for the treatment of many diseases and injuries." Kita, Abstract. Thus, a person of ordinary skill in the art would be motivated to combine the teachings of Kita with

> Pierantozzi, Rojewski, Merion, and Riekstina for the purpose of improving cellular therapies employing MSCs.

Ex. 1007 ¶ 202. We agree that an ordinary artisan would be motivated to look to the teachings of analogous references for information, but to establish obviousness, a party must show "an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418 (2007). Petitioner has not provided sufficient rationale to explain why the ordinary artisan would have been motivated to make the isolated cell with the specific marker profile or why the artisan would have looked to the cited references themselves out of the wide range of analogous references available in the art.

Neither are we persuaded that Pierantozzi, Rojewski, Meiron, or Riekstina address the deficiencies in Petitioner's allegations regarding Kita's teachings, or that they teach limitations [C] or [E]. While we agree that an ordinary artisan would have believed that the art related to MSCs from other tissue sources and cultured in different conditions would be relevant for its teachings and *potentially* applicable to all MSCs, on the record before us, Petitioner has not shown the teachings are interchangeable. Rather, the evidence of record, including Dr. Olson's own testimony, shows that multiple conditions can affect marker expression. *See* Ex. 1089 ¶ 27, Ex. 1014, 175–180, 182. Rojewski in particular acknowledges the unpredictability in MSC marker expression. Ex. 1014, 175–180, 182. Given this unpredictability, we are not persuaded that the ordinary artisan would have reasonably believed that the teachings from Pierantozzi, Rojewski, Meiron, or Riekstina would accurately predict that Kita's MSCs would express the markers observed as expressed or discussed in those references. For instance, we are persuaded that MSCs isolated from

newly-cultured cells obtained from non-umbilical cord tissue as in Pierantozzi would not reliably predict the expression pattern of established cultured umbilical cord-derived subepithelial cells.

For the reasons above, we find that Petitioner has not established that the ordinary artisan would have found it obvious to combine the asserted art or have reasonably believed that the subject matter of claim 1 would result by combining the teachings.

3. Dependent Claims 2–8, 10–13, and 15

Claims 2–8, 10–13, and 15 depend from claim 1. Petitioner's allegations regarding 2–8, 10–13, and 15 rely on its allegations asserted for claim 1. Pet. 61–66. For the reasons explained above, Petitioner has not shown persuasively that the cells isolated by Phan would have the expression pattern of claim 1, or that Pierantozzi, Rojewski, Meiron, or Riekstina cure the deficiencies in Petitioner's allegations regarding Phan's teachings. In addition, for the reasons we address above regarding the incompatibility of teachings from the references, we find that Petitioner has not shown persuasively that the ordinary artisan would have found the subject matter of claims 2–8, 10–13, and 15 obvious or that the artisan would have had an expectation of success in combining the teachings to arrive at the subject matter of claims 2–8, 10–13, and 15.

K. Ground 7 – Obviousness of Claim 14 by Kita, Pierantozzi, Rojewski, Meiron, Riekstina, and Mistry

Claim 14 recites an isolated cell of claim 1 that has differentiated into a cardiomyocyte cell. Petitioner alleges the cited art "all disclose the value of MSCs as a therapeutic for diseases," and that a skilled artisan would have been motivated to combine the teachings of the cited art "to produce cell

therapies for treatment of disease." Pet. 67 (citing Ex. 1007 ¶ 235). Petitioner alleges that the teachings relied upon for showing the obviousness of claim 1 in view of Mistry's teaching of umbilical cord-derived cells made to differentiate into cells with cardiomyocyte markers via treatment with 5-azacytidine would have rendered claim 14 obvious. *Id.* (citing Ex. 1007 ¶ 236).

Patent Owner alleges that Kita does not teach the claimed isolated cell and that Mistry does not teach differentiation into cardiomyocytes, only the expression of cardiac specific genes. PO Resp. 65.

Claim 14 depends from claim 1. For the reasons explained above in Section II.J.2, Petitioner has not shown persuasively that the cells isolated by Kita would have the expression pattern of claim 1, or that Pierantozzi, Rojewski, Meiron, Riekstina, or Mistry cure the deficiencies in Petitioner's allegations regarding Kita's teachings. For this reason, in addition to the reasons we address above regarding the incompatibility of teachings from the references, we find that Petitioner has not shown persuasively that the ordinary artisan would have found the subject matter of claim 14 obvious or that the artisan would have had an expectation of success in combining the teachings to arrive at the subject matter of claim 14.

L. Ground 8 – Obviousness of Claim 9 by Kita, Pierantozzi, Rojewski, Meiron, and Majore

Petitioner alleges that a skilled artisan would have been motivated to combine the teachings of Kita with Pierantozzi, Rojewski, Merion, and Majore "for the purpose of improving cellular therapies employing MSCs." Pet. 67–68 (citing Ex. 1007 ¶ 237). Petitioner alleges the "use of chemically

defined media or human only components was common in the field of MSC biology," and would have been obvious over the cited art. *Id.*

Patent Owner alleges that Majore does not disclose the features of claim 9, and that Kita's culture medium includes 10% fetal bovine serum, making the concept of use of non-animal components not obvious over the cited art.

Claim 9 depends from claim 1. For the reasons explained above in Sections II.G.5 and II.J.2, Petitioner has not shown persuasively that the cells isolated by Kita would have the expression pattern of claim 1, or that Pierantozzi, Rojewski, Meiron, or Majore cure the deficiencies in Petitioner's allegations regarding Kita's teachings. In addition, the evidence of record showing a component of bovine serum in the culture media favors Patent Owner. Ex. 2022 ¶ 173.

For this reason, in addition to the reasons we address above regarding the incompatibility of teachings from the references, we find that Petitioner has not shown persuasively that the ordinary artisan would have found the subject matter of claim 9 obvious or that the artisan would have had an expectation of success in combining the teachings to arrive at the subject matter of claim 9.

M. Petitioner's Motion to Exclude

Petitioner moves to exclude ¶¶ 30–40 of Exhibit 2009 (Declaration of Amit Patel) and Exhibits 2013 (TSOI Quarterly Report) and 2016 (SEC Registration Statement for ImmCelz). Paper 30 ("Pet. MTE"), 1. The relevant paragraphs and documents pertain to Patent Owner's argument that the Challenged Claims are not obvious, including because secondary indicia

of nonobviousness show the claimed subject matter was commercially successful. *See, e.g.*, PO Resp. 69. Because we find Petitioner has not met its burden to show that the Challenged Claims teach or render obvious all of the claim limitations, Petitioner's motion is moot.

III. CONCLUSION

Based on the evidence before us, we determine Petitioner has not shown, by a preponderance of the evidence, that the Challenged Claims of the '176 patent are unpatentable over the asserted prior art.

IV. ORDER

Upon consideration of the record before us, it is:

ORDERED that, pursuant to 35 U.S.C. § 318(a), Challenged Claims 1–15 of U.S. Patent No. 9,803,176 B2 have not been proven unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude ¶¶ 30–40 of Exhibit 2009 and Exhibits 2013 and 2016 is DENIED AS MOOT;

FURTHER ORDERED that Patent Owner's Motion to Exclude Exhibits 1007 and 1089 in their entirety, or, in the alternative, to exclude ¶¶ 92–234 of Exhibit 1007 and ¶¶ 25–87 of Exhibit 1089 is DENIED; and

FURTHER ORDERED that, as this is a Final Written Decision, a party seeking judicial review of the Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not shown Unpatentable
1–13, 15	102	Majore		1–13, 15
14	103	Majore, Mistry		14
1–13, 15	103	Majore, Pierantozzi, Rojewski, Meiron, Riekstina		1–13, 15
14	103	Majore, Pierantozzi, Rojewski, Meiron, Mistry		14
1–15	103	Phan, Pierantozzi, Rojewski, Meiron, Riekstina		1–15
1–8, 10–13, 15	103	Kita, Pierantozzi, Rojewski, Meiron, Riekstina		1–8, 10–13, 15
14	103	Kita, Pierantozzi, Rojewski, Meiron, Riekstina, Mistry		14
9	103	Kita, Pierantozzi, Rojewski, Meiron, Majore		9
Overall Outcome				1–15

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Patent 9,803,176 B2

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(12) **United States Patent**
Patel

(10) **Patent No.: US 9,803,176 B2**
(45) **Date of Patent: Oct. 31, 2017**

(54) **METHODS AND COMPOSITIONS FOR THE CLINICAL DERIVATION OF AN ALLOGENIC CELL AND THERAPEUTIC USES**

(71) Applicant: **Amit Patel**, Salt Lake City, UT (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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C12N 5/077	(2010.01)

(52) **U.S. Cl.**

CPC ***C12N 5/0682*** (2013.01); ***A61K 35/51*** (2013.01); ***C12N 5/0605*** (2013.01); ***C12N 5/0653*** (2013.01); ***C12N 5/0654*** (2013.01); ***C12N 5/0655*** (2013.01); ***C12N 5/0657*** (2013.01); ***C12N 5/0665*** (2013.01)

(58) **Field of Classification Search**

CPC C12N 5/0605
USPC 435/325
See application file for complete search history.

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Primary Examiner — Kara Johnson
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(57) **ABSTRACT**

Various cells, stem cells, and stem cell components, including associated methods of generating and using such cells are provided. In one aspect, for example, an isolated cell that is capable of self-renewal and culture expansion and is obtained from a subepithelial layer of a mammalian umbilical cord tissue. Such an isolated cell expresses at least three cell markers selected from CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, or CD105, and does not express at least three cell markers selected from CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR.

15 Claims, 14 Drawing Sheets

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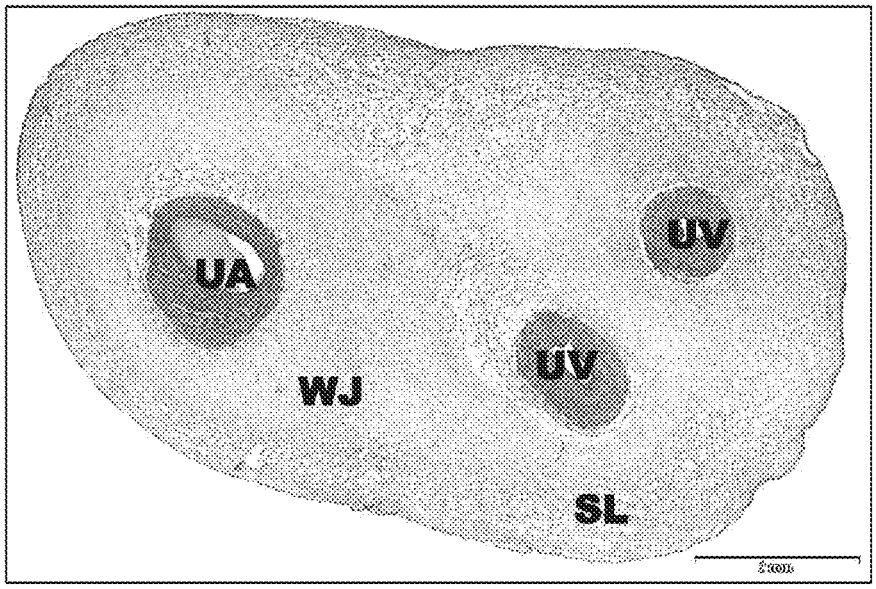


FIG. 1

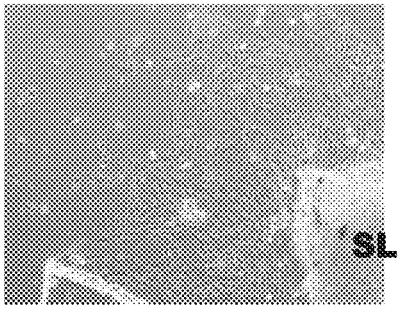


FIG. 2A

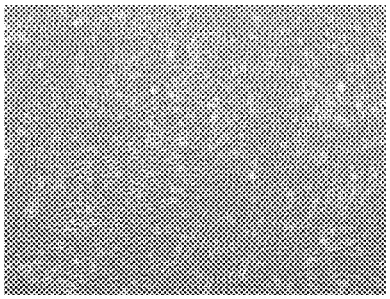


FIG. 2B

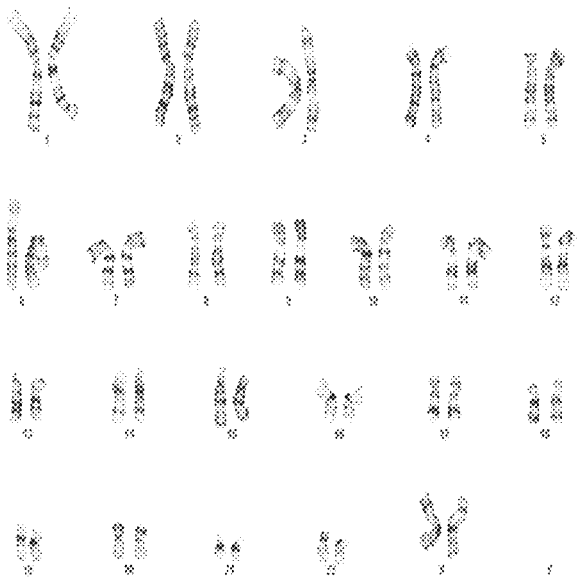


FIG. 2C

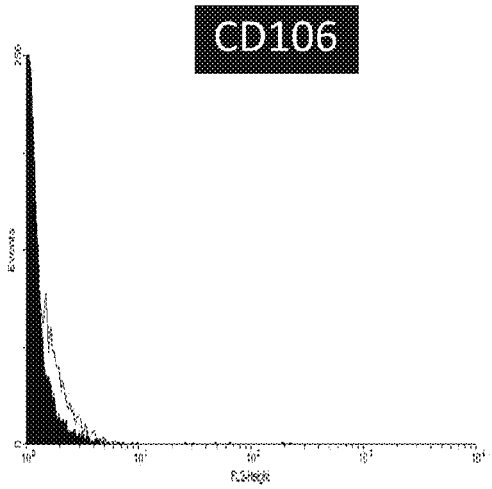
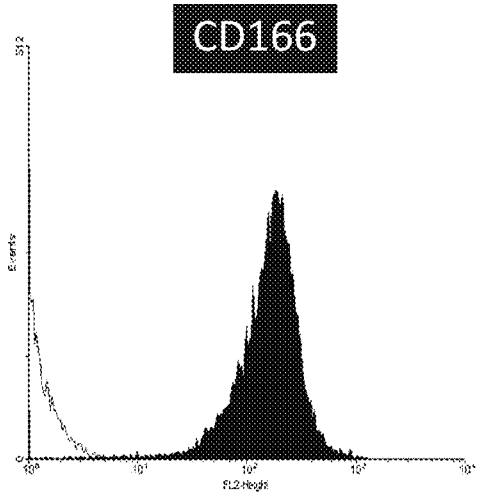


FIG. 3A



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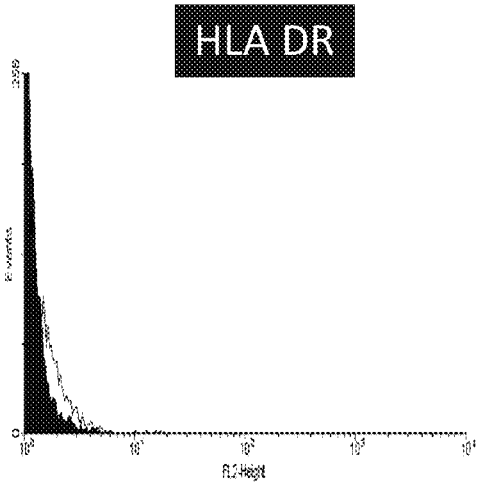

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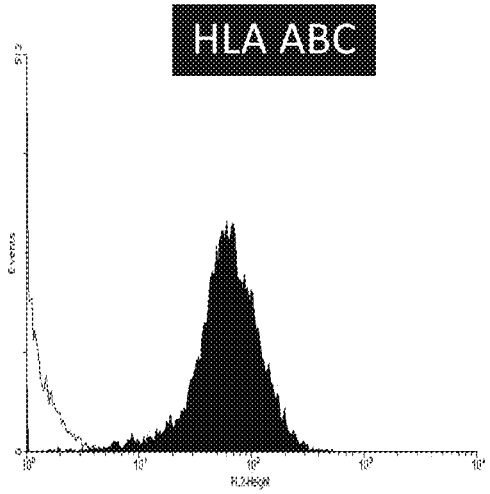
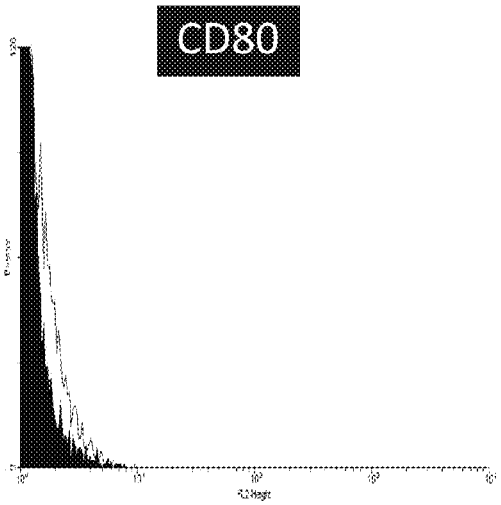


FIG. 3D



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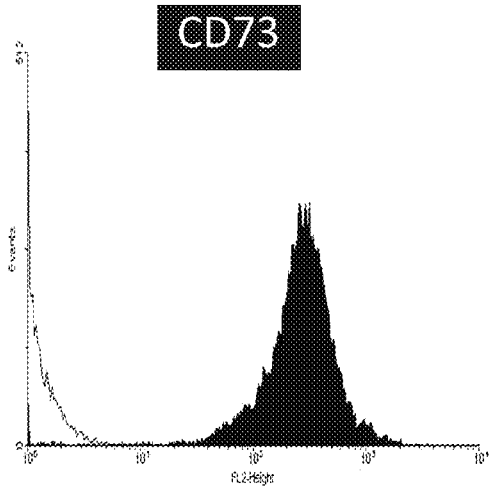

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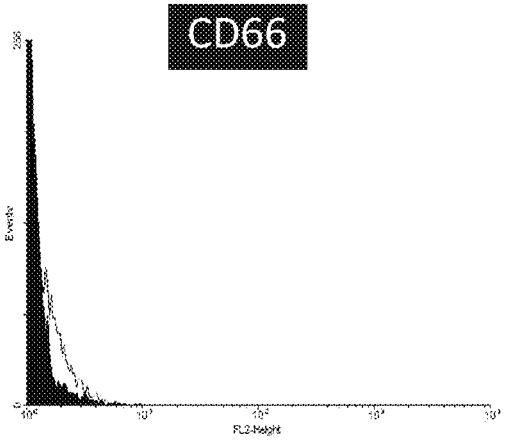

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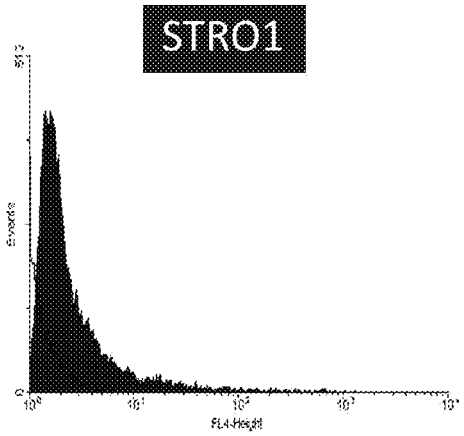

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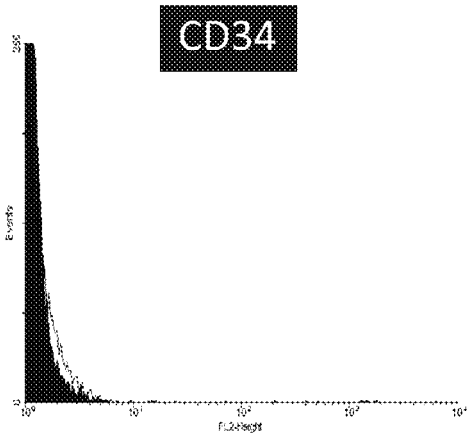
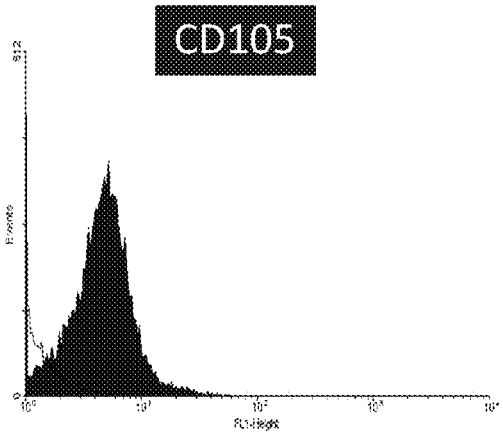


FIG. 3I



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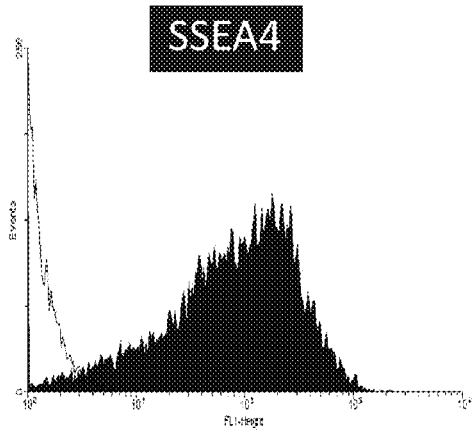

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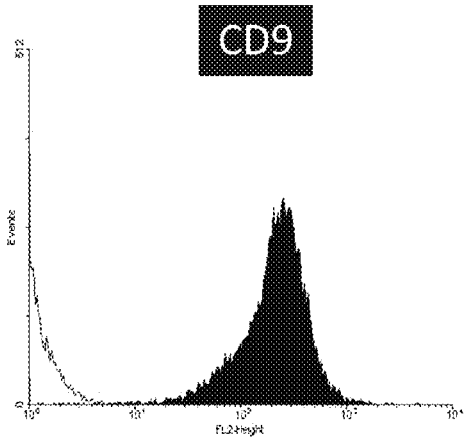

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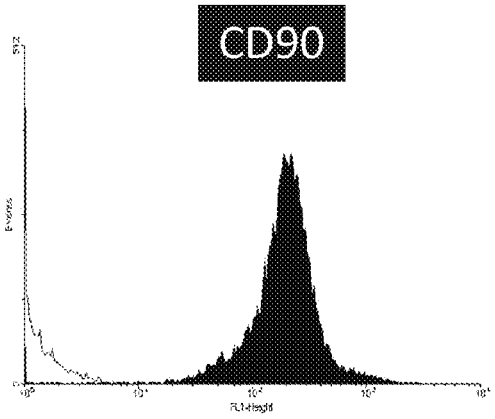

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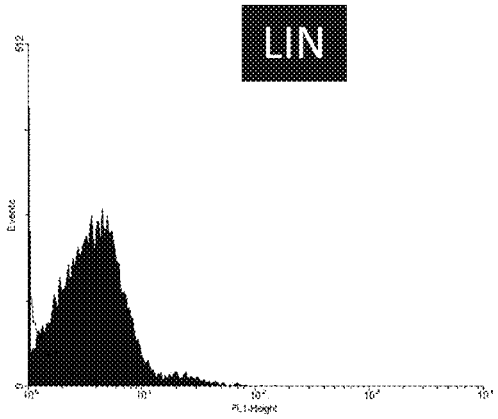

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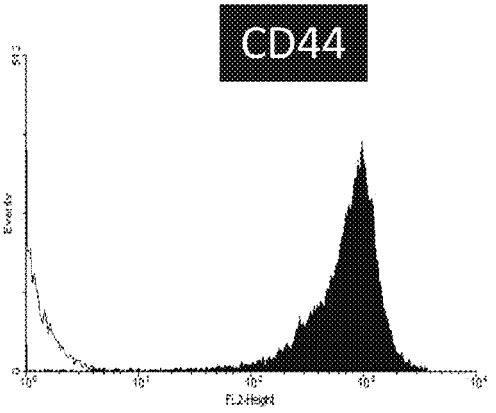
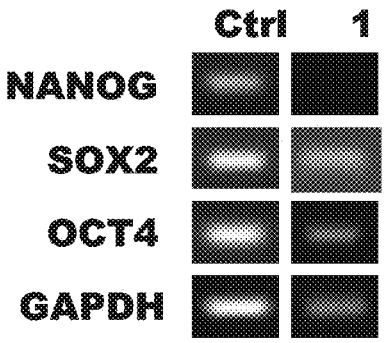


FIG. 3O



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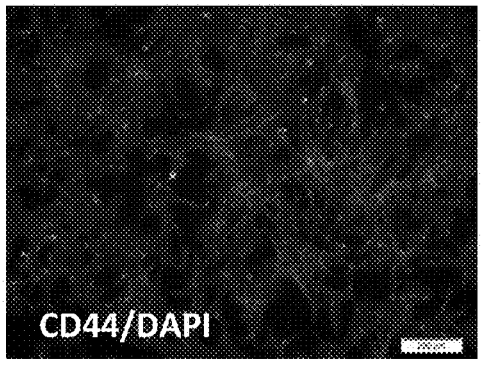
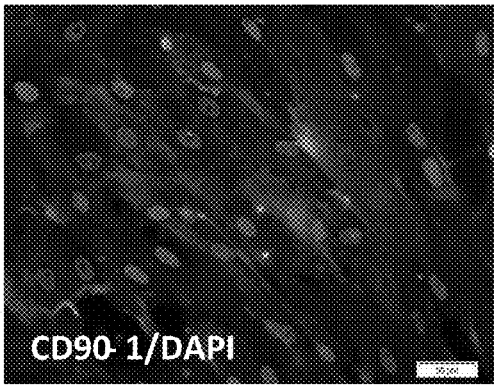


FIG. 4B



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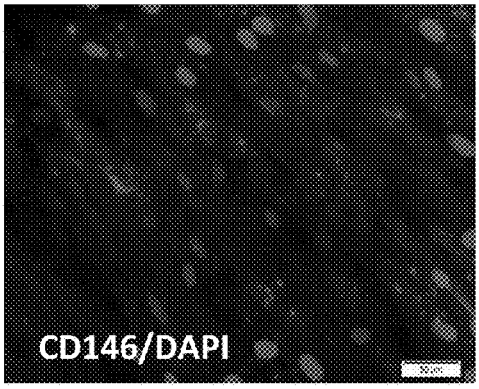


FIG. 4D

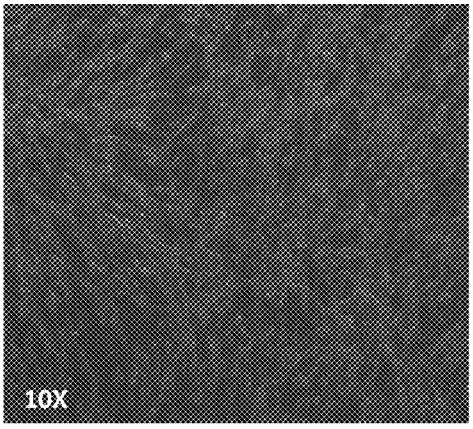


FIG. 5A

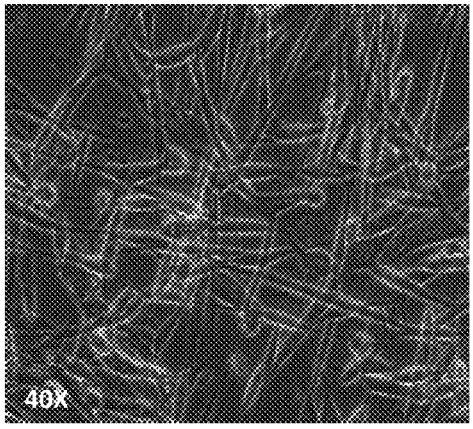


FIG. 5B

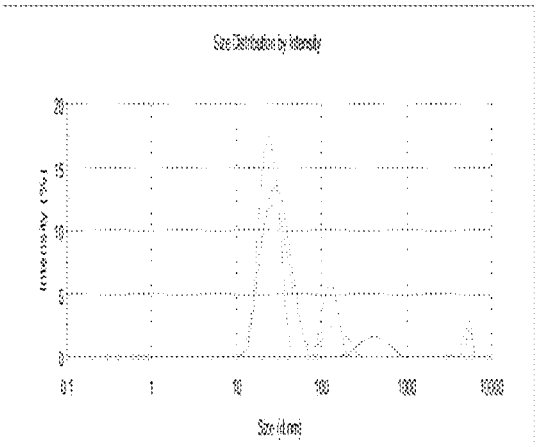


FIG. 6A

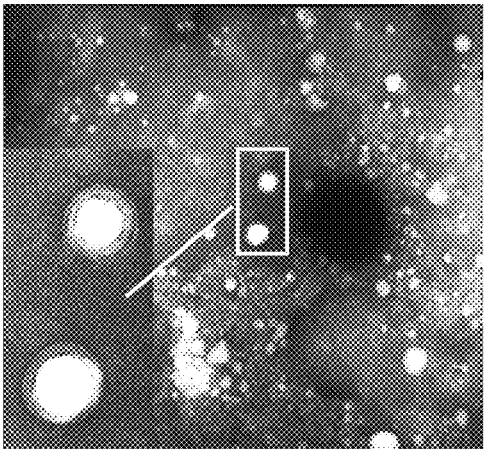


FIG. 6B

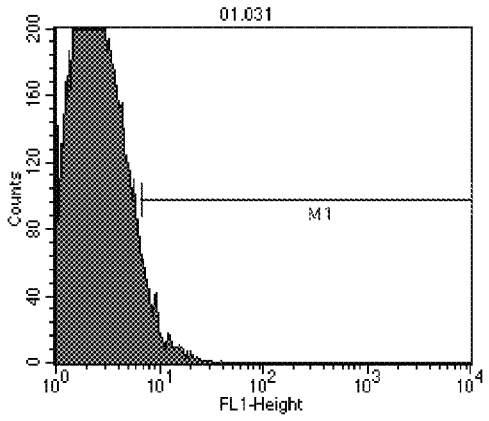


FIG. 6C

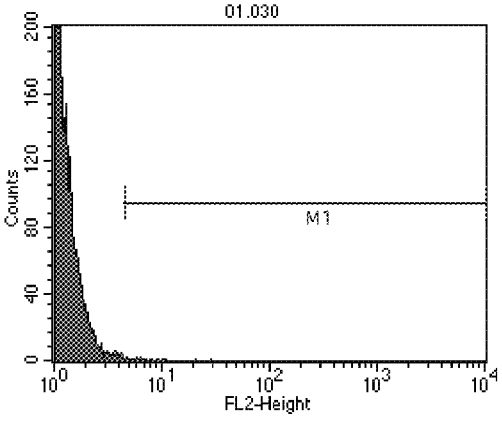
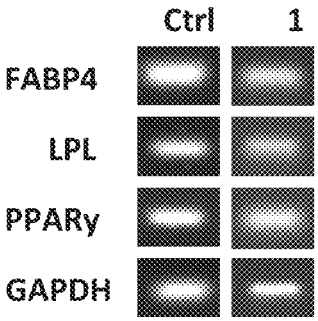


FIG. 6D



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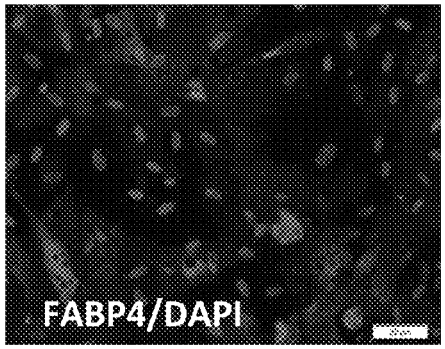

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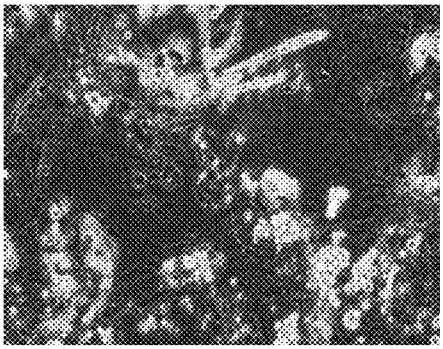

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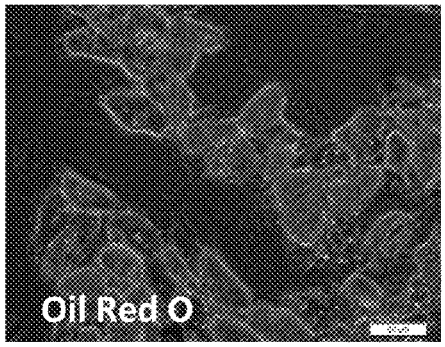

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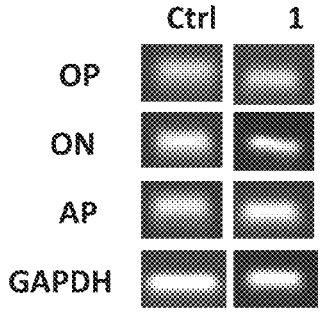
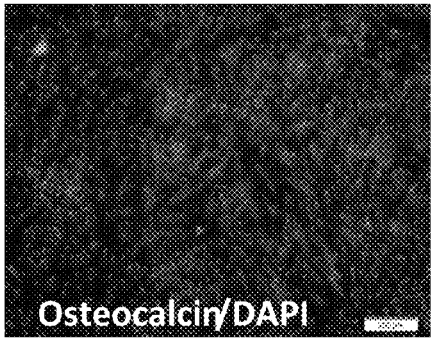


FIG. 8A



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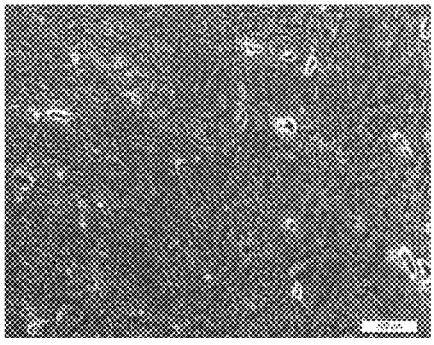

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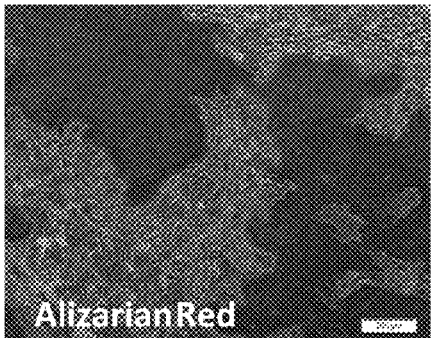

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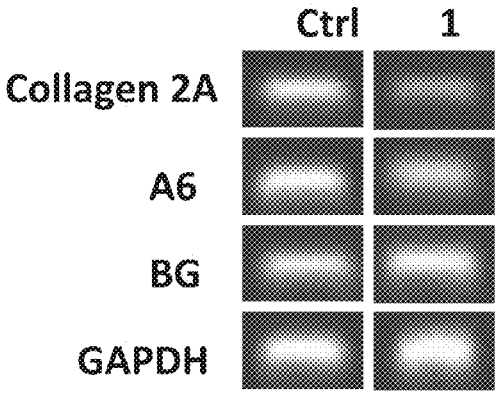
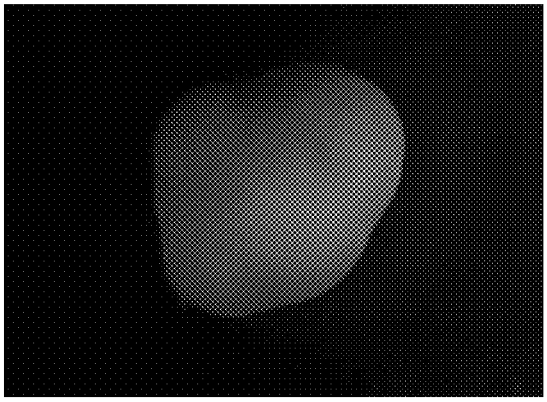


FIG. 9A



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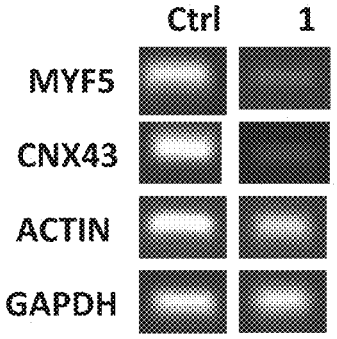


FIG. 10A

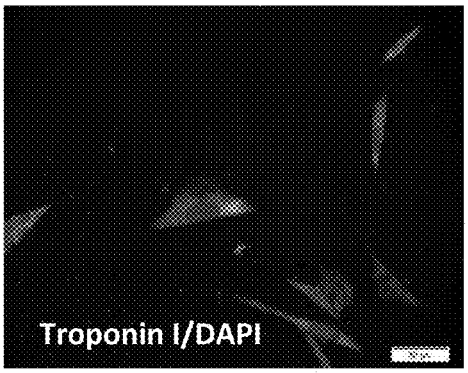


FIG. 10B

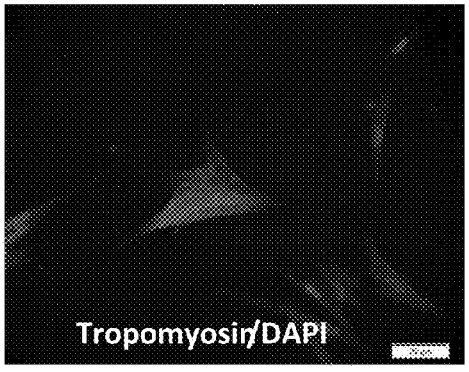
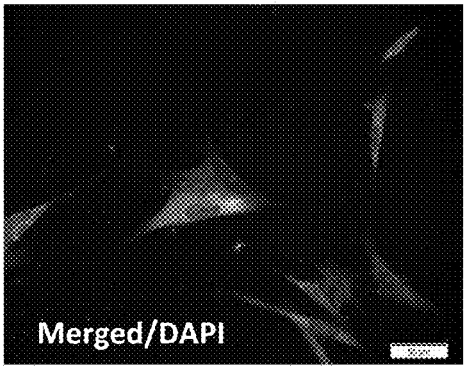


FIG. 10C



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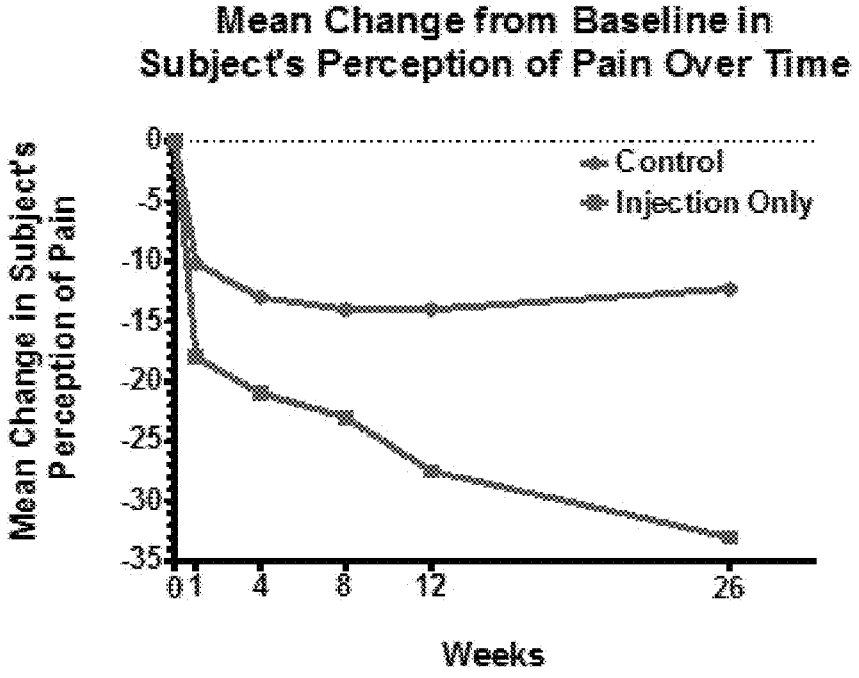


FIG. 11A

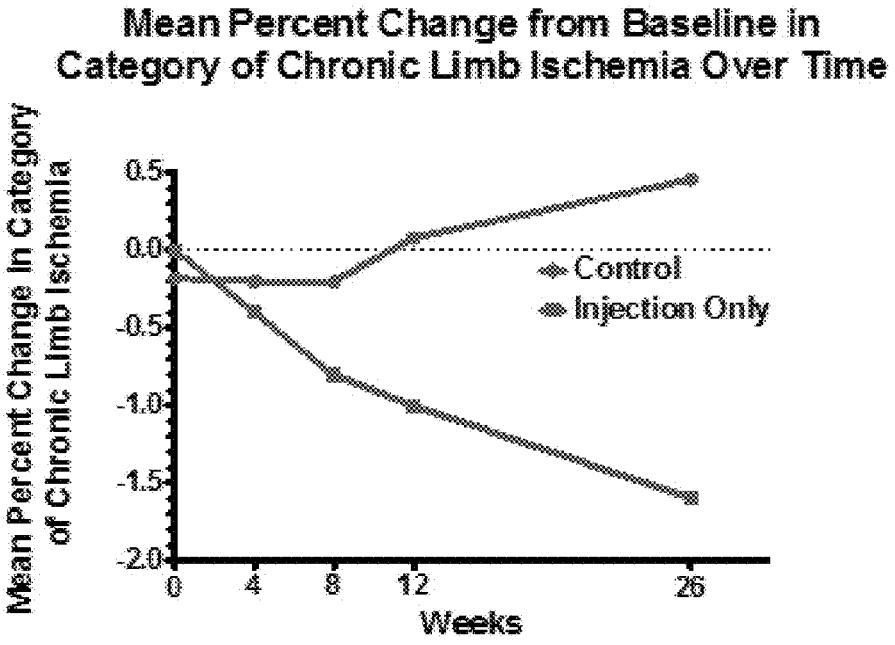
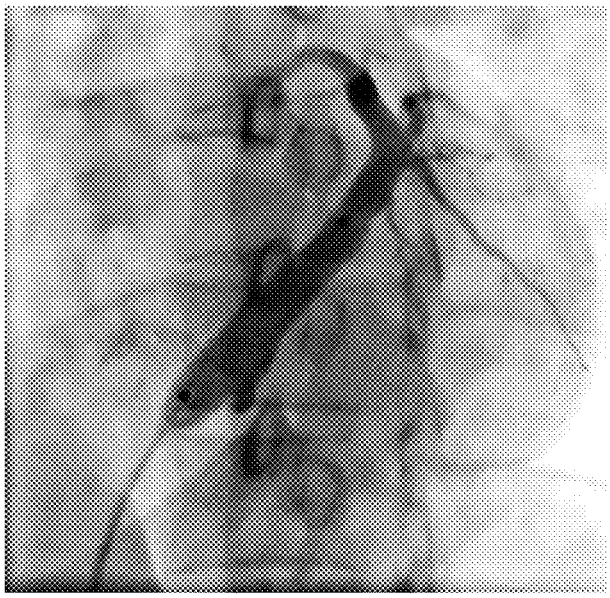


FIG. 11B



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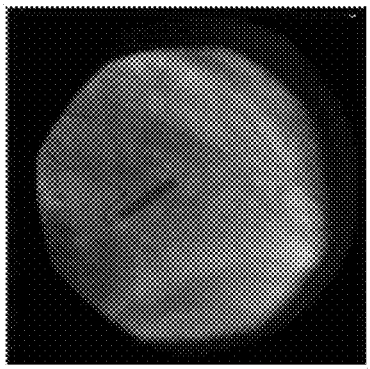

FIG. 13A

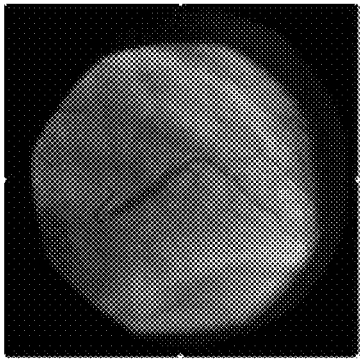

FIG. 13B

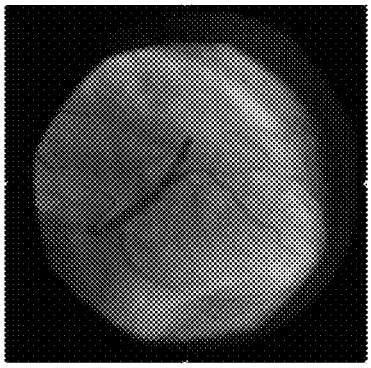

FIG. 13C

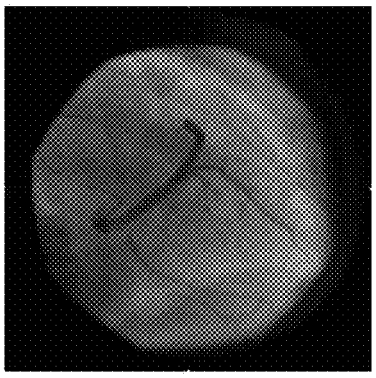

FIG. 13D

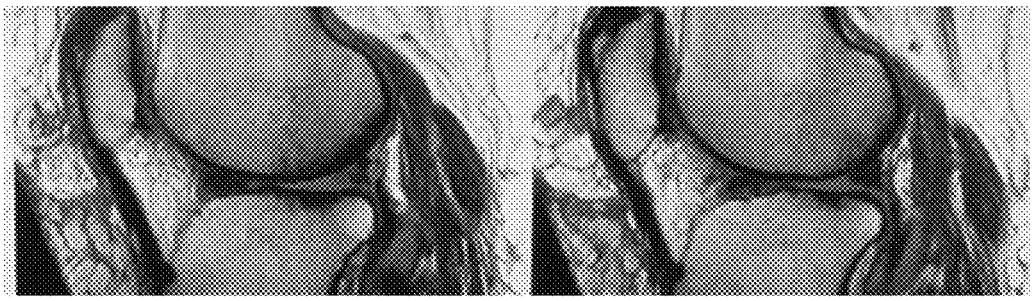

FIG. 14A

FIG. 14B

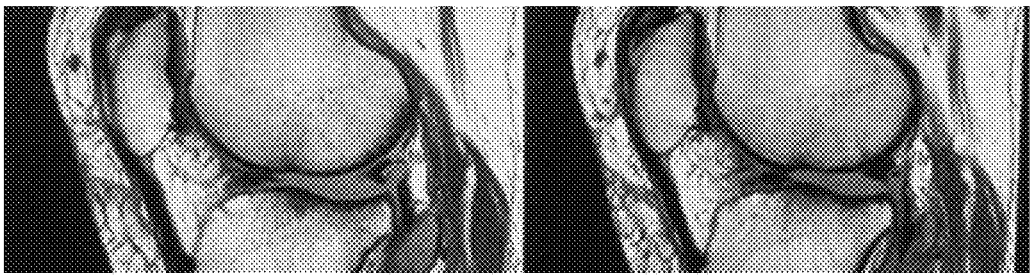

FIG. 14C

FIG. 14D

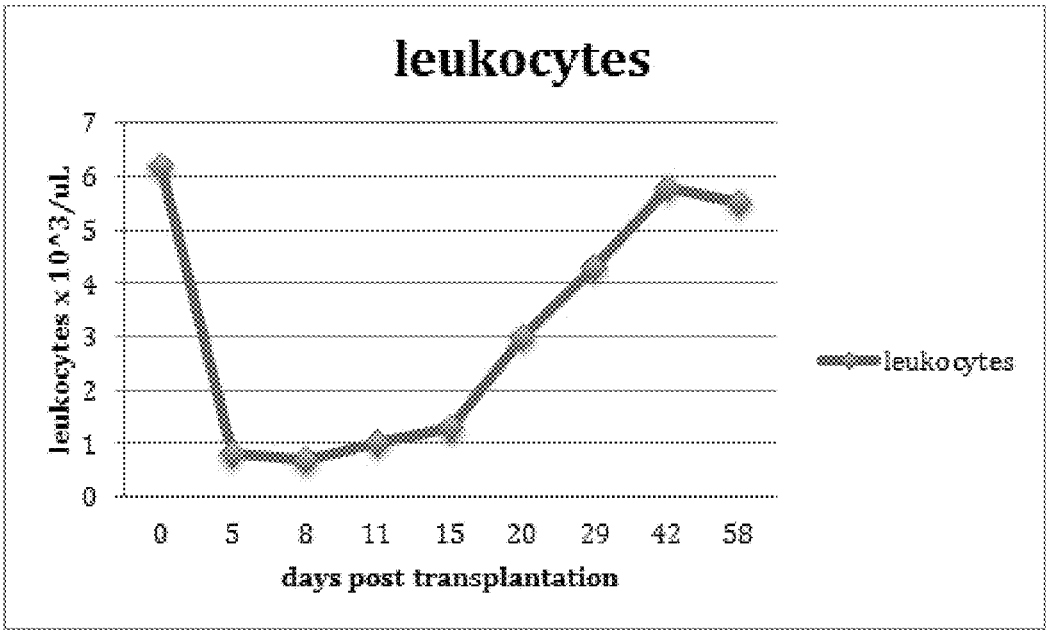

FIG. 15A

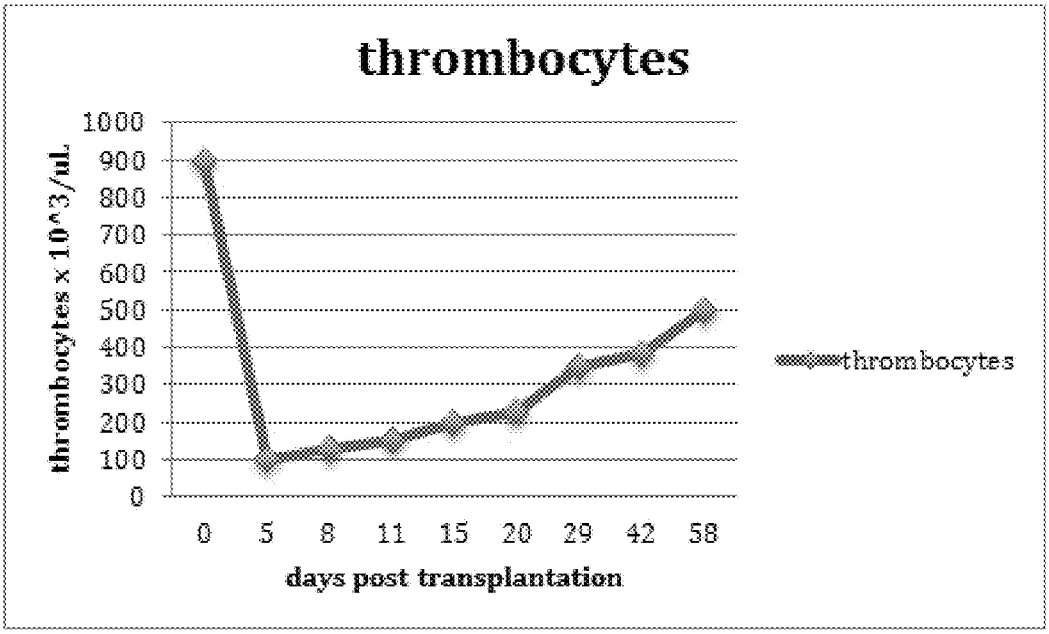

FIG. 15B

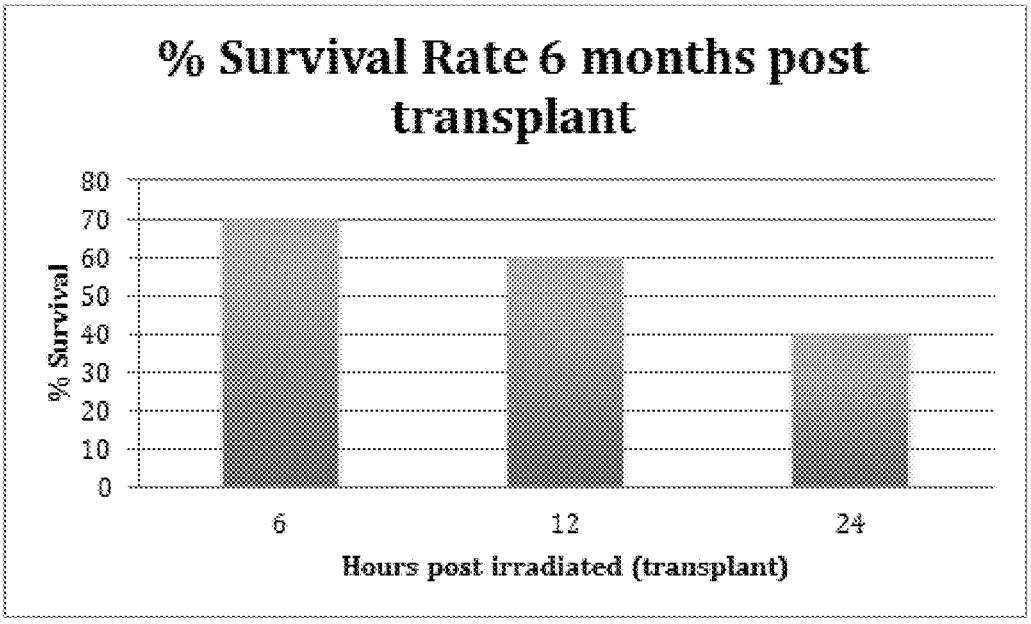
% Survival Rate 6 months post transplant
80
70
60
50
40
30
20
10
0
% Survival
6
12
24
Hours post irradiated (transplant)

FIG. 16

METHODS AND COMPOSITIONS FOR THE CLINICAL DERIVATION OF AN ALLOGENIC CELL AND THERAPEUTIC USES

PRIORITY DATA

This application claims the benefit of U.S. Provisional Patent Application Ser. No. 61/582,070, filed on Dec. 30, 2011, and of U.S. Provisional Patent Application Ser. No. 61/591,211, filed on Jan. 26, 2012, both of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates generally to stem cells and various related aspects thereof. Accordingly, the present invention involves the fields of chemistry, life science, and medicine.

BACKGROUND

Various cell and stem cell populations have been shown to have value for research applications. However, clinical translation of these cell types for human and animal use in therapeutic applications is limited due to a number of reasons, including allogenic issues.

SUMMARY

The present disclosure provides various cells, stem cells, and stem cell components, including associated methods of generating and using such cells. In one aspect, for example, an isolated cell that is capable of self-renewal and culture expansion and is obtained from a subepithelial layer of a mammalian umbilical cord tissue is provided. Such an isolated cell expresses at least three cell markers selected from CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, or CD105, and does not express at least three cell markers selected from CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR. In another aspect, the isolated cell expresses CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, and CD105. In yet another aspect, the isolated cell does not express CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, and HLA-DR. In some aspects, the isolated cell can be positive for SOX2, OCT4, or both SOX2 and OCT4. In a further aspect, the isolated cell can produce exosomes expressing CD63, CD9 or both. It is understood that the present scope includes cultures of isolated cells.

The cells according to aspects of the present disclosure are capable of differentiation into a variety of cell types, and any such cell type is considered to be within the present scope. Non-limiting examples of such cell types can include adipocytes, chondrocytes, osteocytes, cardiomyocytes, endothelial cells, myocytes, and the like, including combinations thereof.

A variety of cells and cellular products can be derived from the isolated cells described herein, and any such cells and cellular products are considered to be within the present scope. In one aspect, for example, the present disclosure provides an isolated exosome derived from the isolated cells described, where the exosome expresses CD63, CD9 or both. In another aspect, an adipocyte cell that has been differentiated from the isolated cells described is provided. In yet another aspect, a chondrocyte cell that has been differentiated from the isolated cells described is provided.

In a further aspect, an osteocyte cell that has been differentiated from the isolated cells described is provided. In yet a further aspect, a cardiomyocyte cell that has been differentiated from the isolated cells described is provided. Furthermore, a culture of differentiated cells derived from the isolated cells described including at least one cell type selected from an adipocyte, a chondrocyte, an osteocyte, or a cardiomyocyte is provided.

In another aspect, the present disclosure provides a method of culturing stem cells from a subepithelial layer of a mammalian umbilical cord. Such a method can include dissecting the subepithelial layer from the umbilical cord, placing the dissected subepithelial layer interior side down on a substrate such that an interior side of the subepithelial layer is in contact with the substrate, and culturing the subepithelial layer on the substrate. The method can additionally include removing explants for primary cell expansion. In one aspect, dissecting the subepithelial layer further includes removing Wharton's Jelly from the umbilical cord.

The subepithelial layer can be cultured in any media capable of producing explants therefrom, and any such medium is considered to be within the present scope. In one specific aspect, however, one such culture medium can include a platelet lysate. In another aspect, the culture media can include human or animal platelet lysate. In yet another aspect, the culture media can be derived from human-free and animal-free ingredients.

The substrate utilized to culture the subepithelial layer can be any substrate capable of deriving explants therefrom. In one aspect, the substrate can be a polymeric matrix. One example of such a polymeric matrix is a culture dish. In one specific aspect, the culture dish can be a cell culture treated plastic, and the subepithelial layer can be placed thereon without any additional pretreatment to the cell culture treated plastic. In another aspect, the substrate can be a semi-solid cell culture substrate. Any type of semi-solid substrate that is capable of supporting the subepithelial layer during the culturing procedure is considered to be within the present scope.

Various culturing conditions are contemplated, and it is understood that such conditions can vary depending on experimental protocol and various desired results. In one aspect, for example, the subepithelial layer can be cultured in a normoxic environment. In another aspect, the subepithelial layer can be cultured in a hypoxic environment. Additionally, in some aspects, the culturing of the subepithelial layer and the removal of the explants can be performed without the use of any enzymes. Furthermore, in some aspects, subculturing of the explants and/or the cells resulting from the explants can be performed without the use of any enzymes.

In yet another aspect of the present disclosure, a method of treating a medical condition responsive to treatment with the isolated cells described herein can include introducing such cells into an individual having the medical condition. These cellular treatments can be utilized to treat any condition for which they are capable providing a benefit. Non-limiting examples of such medical conditions include COPD, diabetes, ischemia, osteoarthritis, orthopedic damage, liver damage, chronic refractory angina, erectile dysfunction, herniated disks, congestive heart failure, asthma, emphysema, wounds, acute radiation syndrome, autoimmune disorders, ischemic organ beds, graft vs. host disease, and the like, including combinations thereof. Additionally, in another aspect, a method of treating a medical condition responsive to treatment with the differentiated cells

described herein can include introducing at least one cell type of the differentiated cells into an individual having the medical condition.

In a further aspect, a method of treating COPD is provided. Such a method can include administering a COPD effective active agent intravenously to a subject to deliver the COPD effective active agent to a lower half of the subject's lung, and administering the COPD effective active agent in an aerosolized form to the subject via ventilation to deliver the COPD effective active agent to an upper half of the subject's lung. In one aspect, the COPD effective active agent includes stem cells. In yet another aspect, the stem cells include cells derived from the subepithelial layer of a mammalian umbilical cord as has been described herein. In one specific aspect, the stem cells can be aerosolized with an aerosolizer to a size of from about 6 to about 200 microns. Additionally, the two types of administration can be delivered sequentially or concomitantly.

In another aspect, the COPD effective active agent can be an active agent other than stem cells. Non-liming examples of such COPD effective active agents can include exosomes, cell lysates, protein extracts derived from cell culture, and the like, including combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows an image of a histological section of umbilical cord identifying the subepethelial layer in accordance with one aspect of the present disclosure.

FIG. **2**A shows explant of cells migrating from the subepithelial layer and karyotyping of cells in accordance with another aspect of the present disclosure.

FIG. **2**B shows explant of cells migrating from the subepithelial layer and karyotyping of cells in accordance with another aspect of the present disclosure.

FIG. **2**C shows karyotyping of cells in accordance with another aspect of the present disclosure

FIG. **3**A shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**B shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**C shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**D shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**E shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**F shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**G shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**H shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**I shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**J shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**K shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**L shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**M shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**N shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **3**O shows FACS analysis of cell determinant markers expressed by cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **4**A shows images of RT-PCR analysis of RNA extracted from cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **4**B shows images of immunocytochemical staining of cells in accordance with another aspect of the present disclosure.

FIG. **4**C shows images of immunocytochemical staining of cells in accordance with another aspect of the present disclosure.

FIG. **4**D shows images of immunocytochemical staining of cells in accordance with another aspect of the present disclosure.

FIG. **5**A shows images of culture of cells or stem cells derived from umbilical cord tissue in semi-solid PRP matrix or PL Lysate in accordance with another aspect of the present disclosure.

FIG. **5**B shows images of culture of cells or stem cells derived from umbilical cord tissue in semi-solid PRP matrix or PL Lysate in accordance with another aspect of the present disclosure.

FIG. **6**A shows extracellular exosome size analysis in accordance with another aspect of the present disclosure.

FIG. **6**B shows an SEM of exosomes in accordance with another aspect of the present disclosure.

FIG. **6**C shows CD63 expression of exosomes produced from cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **6**D shows CD63 expression of exosomes produced from cells or stem cells derived from umbilical cord in accordance with another aspect of the present disclosure.

FIG. **7**A shows images demonstrating differentiation of umbilical cord tissue into adipogeneic lineages in accordance with another aspect of the present disclosure.

FIG. **7**B shows images demonstrating differentiation of umbilical cord tissue into adipogeneic lineages in accordance with another aspect of the present disclosure.

FIG. **7**C shows images demonstrating differentiation of umbilical cord tissue into adipogeneic lineages in accordance with another aspect of the present disclosure.

FIG. **7**D shows images demonstrating differentiation of umbilical cord tissue into adipogeneic lineages in accordance with another aspect of the present disclosure.

FIG. **8**A shows images demonstrating differentiation of umbilical cord tissue into osteogenic lineages in accordance with another aspect of the present disclosure.

FIG. **8**B shows images demonstrating differentiation of umbilical cord tissue into osteogenic lineages in accordance with another aspect of the present disclosure.

FIG. **8**C shows images demonstrating differentiation of umbilical cord tissue into osteogenic lineages in accordance with another aspect of the present disclosure.

FIG. **8**D shows images demonstrating differentiation of umbilical cord tissue into osteogenic lineages in accordance with another aspect of the present disclosure.

FIG. **9**A shows an image demonstrating differentiation of umbilical cord tissue into Chondrogenic lineages in accordance with another aspect of the present disclosure.

FIG. **9**B shows an image demonstrating differentiation of umbilical cord tissue into Chondrogenic lineages in accordance with another aspect of the present disclosure.

FIG. **10**A shows an image demonstrating differentiation of umbilical cord tissue into cardiogenic lineages in accordance with another aspect of the present disclosure.

FIG. **10**B shows an image demonstrating differentiation of umbilical cord tissue into cardiogenic lineages in accordance with another aspect of the present disclosure.

FIG. **10**C shows an image demonstrating differentiation of umbilical cord tissue into cardiogenic lineages in accordance with another aspect of the present disclosure.

FIG. **10**D shows an image demonstrating differentiation of umbilical cord tissue into cardiogenic lineages in accordance with another aspect of the present disclosure.

FIG. **11**A shows data relating to chronic limb ischemia and pain perception over time in accordance with another aspect of the present disclosure.

FIG. **11**B shows data relating to chronic limb ischemia and pain perception over time in accordance with another aspect of the present disclosure.

FIG. **12** shows an image of an angiogram demonstrating delivery of cells into the heart in accordance with another aspect of the present disclosure.

FIG. **13**A shows an image in a series of images of an angiogram demonstrating delivery of cells into the heart in accordance with another aspect of the present disclosure.

FIG. **13**B shows an image in a series of images of an angiogram demonstrating delivery of cells into the heart in accordance with another aspect of the present disclosure.

FIG. **13**C shows an image in a series of images of an angiogram demonstrating delivery of cells into the heart in accordance with another aspect of the present disclosure.

FIG. **13**D shows an image in a series of images of an angiogram demonstrating delivery of cells into the heart in accordance with another aspect of the present disclosure.

FIG. **14**A shows an image of a series of images of the knee of an 80 year old female prior to and following the delivery of stem cells into the intraarticular space in accordance with another aspect of the present disclosure.

FIG. **14**B shows an image of a series of images of the knee of an 80 year old female prior to and following the delivery of stem cells into the intraarticular space in accordance with another aspect of the present disclosure.

FIG. **14**C shows an image of a series of images of the knee of an 80 year old female prior to and following the delivery of stem cells into the intraarticular space in accordance with another aspect of the present disclosure.

FIG. **14**D shows an image of a series of images of the knee of an 80 year old female prior to and following the delivery of stem cells into the intraarticular space in accordance with another aspect of the present disclosure.

FIG. **15**A shows data relating to acute radiation syndrome in accordance with another aspect of the present disclosure.

FIG. **15**B shows data relating to acute radiation syndrome in accordance with another aspect of the present disclosure.

FIG. **16** shows data relating to acute radiation syndrome in accordance with another aspect of the present disclosure.

DETAILED DESCRIPTION

Before the present disclosure is described herein, it is to be understood that this disclosure is not limited to the particular structures, process steps, or materials disclosed herein, but is extended to equivalents thereof as would be recognized by those ordinarily skilled in the relevant arts. It should also be understood that terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting.

Definitions

The following terminology will be used in accordance with the definitions set forth below.

It should be noted that, as used in this specification and the appended claims, the singular forms "a," and, "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes one or more of such cells and reference to "the flask" includes reference to one or more of such flasks.

As used herein, the term "isolated cell" refers to a cell that has been isolated from the subepithelial layer of a mammalian umbilical cord.

As used herein, the term "substantially" refers to the complete or nearly complete extent or degree of an action, characteristic, property, state, structure, item, or result. For example, an object that is "substantially" enclosed would mean that the object is either completely enclosed or nearly completely enclosed. The exact allowable degree of deviation from absolute completeness may in some cases depend on the specific context. However, generally speaking the nearness of completion will be so as to have the same overall result as if absolute and total completion were obtained. The use of "substantially" is equally applicable when used in a negative connotation to refer to the complete or near complete lack of an action, characteristic, property, state, structure, item, or result. For example, a composition that is "substantially free of" particles would either completely lack particles, or so nearly completely lack particles that the effect would be the same as if it completely lacked particles. In other words, a composition that is "substantially free of" an ingredient or element may still actually contain such item as long as there is no measurable effect thereof.

As used herein, the term "about" is used to provide flexibility to a numerical range endpoint by providing that a given value may be "a little above" or "a little below" the endpoint.

As used herein, a plurality of items, structural elements, compositional elements, and/or materials may be presented in a common list for convenience. However, these lists should be construed as though each member of the list is individually identified as a separate and unique member. Thus, no individual member of such list should be construed as a de facto equivalent of any other member of the same list solely based on their presentation in a common group without indications to the contrary.

Concentrations, amounts, and other numerical data may be expressed or presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and thus should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. As an illustration, a numerical range of "about 1 to about 5" should be interpreted to include not only the explicitly recited values of about 1 to about 5, but also include individual values and sub-ranges within the indicated range. Thus, included in this numerical range are individual values such as 2, 3, and 4 and sub-ranges such as from 1-3, from 2-4, and from 3-5, etc., as well as 1, 2, 3, 4, and 5, individually.

This same principle applies to ranges reciting only one numerical value as a minimum or a maximum. Furthermore, such an interpretation should apply regardless of the breadth of the range or the characteristics being described.

The Disclosure

The present disclosure presents a novel discovery of an allogenic cell or stem cell population that can be used for treating a wide range of conditions. In addition this disclosure describes a novel media and method of culturing these cells without, in some cases, the use of animal products or enzymes. As such, cells, stem cells, cell cultures, and associated methods, including methods of isolating, culturing, developing, or otherwise producing these cells are provided. The scope of the present disclosure additionally encompasses research and therapeutic uses of such cell and cell cultures, including compounds derived therefrom.

As one example, the cell and stem cell populations and compounds derived from these populations may be used in allogenic applications to treat a wide range of conditions including, but not limited to, cardiac, orthopedic, autoimmune, diabetes, cardio vascular disorders, neurological, erectile dysfunction, spinal cord injuries, herniated disks, critical limb ischemia, hypertension, wound healing, ulcers, chronic obstructive lung disease, acute radiation syndrome, graft vs. host disease, ischemic organ beds and the like. Also described are methods of producing cell and stem cell populations and compounds that may be used for drug discovery and development, as well as toxicology testing. Examples of compounds derived from these cell and stem cell populations are small vesicles that contain proteins, RNA, micro RNAs, and the like, that are specific to the cell and stem cell populations.

In one aspect, an isolated cell obtained from a subepithelial layer of a mammalian umbilical cord tissue capable of self-renewal and culture expansion is provided. Such a cell is capable of differentiation into a cell type such as, in one aspect for example, adipocytes, chondrocytes, osteocytes, cardiomyocytes, and the like. In another aspect, non-limiting examples of such cell types can include white, brown, or beige adipocytes, chondrocytes, osteocytes, cardiomyocytes, endothelial cells, myocytes, and the like, including combinations thereof. Other examples of such cell types can include neural progenitor cells, hepatocytes, islet cells, renal progenitor cells, and the like.

A cross section of a human umbilical cord is shown in FIG. **1**, which shows the umbilical artery (UA), the umbilical veins (UV), the Wharton's Jelly (WJ), and the subepithelial layer (SL). Isolated cells from the SL can have a variety of characteristic markers that distinguish them from cell previously isolated from umbilical cord samples. It should be noted that these isolated cells are not derived from the Wharton's Jelly, but rather from the SL.

Various cellular markers that are either present or absent can be utilized in the identification of these SL-derived cells, and as such, can be used to show the novelty of the isolated cells. For example, in one aspect, the isolated cell expresses at least three cell markers selected from CD29, CD73, CD90, CD146, CD166, SSEA4, CD9, CD44, CD146, or CD105, and the isolated cell does not express at least three cell markers selected from CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR. In another aspect, the isolated cell expresses at least five cell markers selected from CD29, CD73, CD90, CD146, CD166, SSEA4, CD9, CD44, CD146, or CD105. In another aspect, the isolated cell expresses at least eight cell markers selected from CD29, CD73, CD90, CD146, CD166, SSEA4, CD9, CD44, CD146, or CD105. In a yet another aspect, the isolated cell expresses at least CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, and CD105. In another aspect, the isolated cell does not express at least five cell markers selected from CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR. In another aspect, the isolated cell does not express at least eight cell markers selected from CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR. In yet another aspect, the isolated cell does not express at least CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, and HLA-DR. Additionally, in some aspects, the isolated cell can be positive for SOX2, OCT4, or both SOX2 and OCT4. In a further aspect, the isolated cell can produce exosomes expressing CD63, CD9, or both CD63 and CD9.

A variety of techniques can be utilized to extract the isolated cells of the present disclosure from the SL, and any such technique that allows such extraction without significant damage to the cells is considered to be within the present scope. In one aspect, for example, a method of culturing stem cells from the SL of a mammalian umbilical cord can include dissecting the subepithelial layer from the umbilical cord. In one aspect, for example, umbilical cord tissue can be collected and washed to remove blood, Wharton's Jelly, and any other material associated with the SL. For example, in one non-limiting aspect the cord tissue can be washed multiple times in a solution of Phosphate-Buffered Saline (PBS) such as Dulbecco's Phosphate-Buffered Saline (DPBS). In some aspects the PBS can include a platelet lysate (i.e. 10% PRP lysate of platelet lysate). Any remaining Wharton's Jelly or gelatinous portion of the umbilical cord can then be removed and discarded. The remaining umbilical cord tissue (the SL) can then be placed interior side down on a substrate such that an interior side of the SL is in contact with the substrate. An entire dissected umbilical cord with the Wharton's Jelly removed can be placed directly onto the substrate, or the dissected umbilical cord can be cut into smaller sections (e.g. 1-3 mm) and these sections can be placed directly onto the substrate.

A variety of substrates are contemplated upon which the SL can be placed. In one aspect, for example, the substrate can be a solid polymeric material. One example of a solid polymeric material can include a cell culture dish. The cell culture dish can be made of a cell culture treated plastic as is known in the art. In one specific aspect, the SL can be placed upon the substrate of the cell culture dish without any additional pretreatment to the cell culture treated plastic. In another aspect, the substrate can be a semi-solid cell culture

substrate. Such a substrate can include, for example, a semi-solid culture medium including an agar or other gelatinous base material.

Following placement of the SL on the substrate, the SL is cultured in a suitable medium. In some aspects it is preferable to utilized culture media that is free of animal and human components or contaminants. As one example, FIG. **2** shows the culturing of cells from the SL. As can be seen in FIG. **2**A, at three days post plating of the SL, cells have begun to migrate. FIG. **2**B shows cells after 6 days of culture in animal free media. Furthermore, FIG. **2**C shows the karyotype of cells following passage 12. As has been described, the cells derived from the SL have a unique marker expression profile. Data showing a portion of this profile is shown in FIGS. **3**A-O.

The culture can then be cultured under either normoxic or hypoxic culture conditions for a period of time sufficient to establish primary cell cultures. (e.g. 3-7 days in some cases). After primary cell cultures have been established, the SL tissue is removed and discarded. Cells or stem cells are further cultured and expanded in larger culture flasks in either a normoxic or hypoxic culture conditions. While a variety of suitable cell culture media are contemplated, in one non-limiting example the media can be Dulbecco's Modified Eagle Medium (DMEM) glucose (500-6000 mg/mL) without phenol red, 1× glutamine, 1× NEAA, and 0.1-20% PRP lysate or platelet lysate. Another example of suitable media can include a base medium of DMEM low glucose without phenol red, 1× glutamine, 1× NEAA, 1000 units of heparin and 20% PRP lysate or platelet lysate. In another example, cells can be cultured directly onto a semi-solid substrate of DMEM low glucose without phenol red, 1× glutamine, 1× NEAA, and 20% PRP lysate or platelet lysate. In a further example, culture media can include a low glucose medium (500-1000 mg/mL) containing 1× Glutamine, 1× NEAA, 1000 units of heparin. In some aspects, the glucose can be 1000-4000 mg/mL, and in other aspects the glucose can be high glucose at 4000-6000 mg/mL. These media can also include 0.1%-20% PRP lysate or platelet lysate. In yet a further example, the culture medium can be a semi-solid with the substitution of acid-citrate-dextrose ACD in place of heparin, and containing low glucose medium (500-1000 mg/mL), intermediate glucose medium (1000-4000 mg/mL) or high glucose medium (4000-6000 mg/mL), and further containing 1× Glutamine, 1× NEAA, and 0.1%-20% PRP lysate or platelet lysate. In some aspects, the cells can be derived, subcultured, and/or passaged using TrypLE. In another aspect, the cells can be derived, subcultured, and/or passaged without the use of TrypLE or any other enzyme.

FIG. **4** shows data relating to various genetic characteristics of the cells isolated from the SL tissue. FIG. **4**A shows that isolated SL cells (lane 1) are positive for SOX2 and OCT4, and are negative for NANOG as compared to control cells (Ctrl). FIG. **4**B shows a DAPI stained image of cultured SL cells demonstrating that such cells are positive for CD44. FIG. **4**C shows a DAPI stained image of cultured SL cells demonstrating that such cells are positive for CD90. FIG. **4**D shows a DAPI stained image of cultured SL cells demonstrating that such cells are positive for CD 146.

In one aspect, SL cells can be cultured from a mammalian umbilical cord in a semi-solid PRP Lysate or platelet lysate substrate. Such cells can be cultured directly onto a plastic coated tissue culture flask as has been described elsewhere herein. After a sufficient time in either normoxic or hypoxic culture environments the media is changed and freshly made semi-solid PRP lysate or platelet lysate media is added to the culture flask. The flask is continued to be cultured in either a normoxic or hypoxic culture environment. The following day the media becomes a semi-solid PRP-lysate or platelet lysate matrix. The cells can be continued to be cultured in this matrix being until further use. FIGS. **5**A and B show SL cells growing in a semi-solid PRPL or PL gel at 10× and 40× magnifications. In one specific aspect, ingredients for a semi solid culture can include growth factors for expanded cell culture of differentiation. Non-limiting examples can include FGF, VEGF, FNDC5, 5-azacytidine, TGF-Beta1, TGF Beta2, insulin, ITS, IGF, and the like, including combinations thereof.

In some cases, allogenic confirmation of SL cells, either differentiated or undifferentiated, can be highly beneficial, particularly for therapeutic uses of the cells. In such cases, mixed lymphocyte reactions can be performed on the cells to confirm the allogenic properties of the cells. In certain aspects, a cell derived as described herein does not cause a mixed lymphocyte response or T-cell proliferation.

In certain aspects, a cell derived as described herein can be recombinantly modified to express one or more genes and or proteins. In one technique, a gene or genes can be incorporated into an expression vector. Approaches to deliver a gene into the cell can include without limitation, viral vectors, including recombinant retroviruses, adenoviruses, adeno-associated virus, lentivirus, poxivirus, alphavirus, herpes simplex virus-1, recombinant bacterial, eukaryotic plasmids, and the like, including combinations thereof. Plasmid DNA may be delivered naked or with the help of exosomes, cationic liposomes or derivatized (antibody conjugated) polylysine conjugates, gramicidin S, artificial viral envelopes, other intracellular carriers, as well as direct injection of the genes. In some aspects, non-viral gene delivery methods can be used, such as for example, scaffold/matrix attached region (S/MAR)-based vector.

Furthermore, in some aspects, isolated SL cells can be used to produce an exosome population. These exosome populations can be utilized for a variety of research and therapeutic uses. In one aspect, for example, cells are cultured as described in either a normoxic or hypoxic culture environment and supernatants are collected at each media change. Exosomes can then be purified from the supernatants using an appropriate purification protocol. One not-limiting example of such a protocol is the ExoQuick isolation system by SYSTEMBIO. Purified exosomes can be utilized for further manipulation, targeting, and therapeutic use. The exosomes specific to the SL cells are positive for CD63 expression. FIG. **6**A shows an analysis of the size of exosomes obtained as has been described, and FIG. **6**B shows and electron microscope image of a sampling of exosomes. Additionally, FIGS. **6**C-D show CD63 expression of exosomes produced from cells or stem cells derived from umbilical cord.

In some aspects, the isolated cells and cell cultures can be utilized as-is upon isolation from the SL tissue. In other aspects, the isolated cells can be differentiated into other cell types. It should be noted that any useful cell type that can be derived from the cells isolated from SL tissue are considered to be within the present scope. Non-limiting examples of such cell types include adipocytes, chondrocytes, osteocytes, cardiomyocytes, and the like. Differentiation can be induced by exposing the cells to chemicals, growth factors, supernatants, synthetic or naturally occurring compounds, or any other agent capable of transforming the cells. In one aspect, for example, the isolated cells can be differentiated into adipocytes, as is shown in FIG. **7**.

Any technique for differentiation of SL cells into adipocytes is considered to be within the present scope. One non-limiting example used for adipogenic differentiation includes SL cells cultured in the presence of StemPro Adipogenic Differentiation media (Life Technologies). FIG. **7**A shows differentiated SL cells that are positive for the adipogenic markers FABP4, LPL, and PPARy (lane 1). For adipogenic differentiation, confirmation was determined by Oil Red O staining and FABP4 immunocytochemistry.

FIG. **7**B shows an image of DAPI stained cells showing FABP4 markers. FIG. **7**C shows unstained cells and FIG. **7**D shows Oil Red O staining demonstrating the storage of fats in the cells.

For osteogenic differentiation of SL cells, one non-limiting technique cultures such cells in the presence of StemPro Osteogenic Differentiation media (Life Technologies). As is shown in FIG. **8**A, for example, differentiated SL cells are positive for the osteogenic markers OP, ON, and AP (lane 1). For osteogenic differentiation, confirmation was determined by Alizarin red staining and osteocalcin immunocytochemistry. FIG. **8**B shows an image of DAPI stained cells showing the presence of osteocalcin. FIG. **8**C shows unstained cells and FIG. **8**D shows an image of cells stained with alizarin red demonstrating the presence of calcific deposition in the cells.

For chondrogenic differentiation of SL cells, one non-limiting technique cultures SL cells in the presence of StemPro Chondrogenic Differentiations media (Life Technologies). As is shown in FIG. **9**A, differentiated SL cells are positive for chondrogenic markers Collagen 2A, A6, and BG (lane 1). For chondrogenic differentiation, confirmation was determined by Von Kossa staining. FIG. **9**B shows Alcian blue staining of a chondrocyte pellet.

For cardiogenic differentiation of SL cells, one non-limiting technique cultures cells in the presence of DMEM low glucose without phenol red, 1× glutamine, 1× NEAA and 10% PRP lysate or platelet lysate with 5-10 μM 5-AZA-2'-deoxycytidine.

As is shown in FIG. **10**A, differentiated SL cells are positive for the cardiogenic markers MYF5, CNX43, and ACTIN (lane 1). For cardiogenic differentiation, confirmation was determined by staining for ANP, tropomyosin, and troponin 1. FIG. **10**B shows an image of DAPI stained cells demonstrating the presence of Troponin 1. FIG. **10**C shows an image of DAPI stained cells demonstrating the presence of tropomyosin. FIG. **10**D shows a merged image of the images from FIGS. **10**B and **10**C.

In yet another aspect, a method of treating a medical condition is provided. In some embodiments, such a method can include introducing cells described herein into an individual having the medical condition. Cells can be delivered at various doses such as, without limitation, from about 500,000 to about 1,000,000,000 cells per dose. In some aspects, the cell dosage range can be calculated based on the subject's weight. In certain aspects, the cell range is calculated based on the therapeutic use or target tissue or method of delivery. Non-limiting examples of medical conditions can include COPD, diabetes, ischemia, osteoarthritis, orthopedic damage, liver damage, chronic refractory angina, congestive heart failure, asthma, emphysema, wounds, erectile dysfunction, spinal cord injuries, herniated disks, acute radiation syndrome, neurological disorders, graft vs. host disease, autoimmune disorders, renal failure, autoimmune disorders, and the like, including combinations thereof. The treatment can include introducing cells into a region of the subject where the medical condition can be treated. The cells can be delivered intramuscularly, intravenously, intraarterially, subcutaneously, surgically, intrathecally, intraperitoneally, intranasally, orally, topically, rectally, vaginally, via aspiration, and the like, including combinations thereof. Additionally, in one aspect, undifferentiated SL cells can be delivered to the subject to treat the medical condition. In another aspect, differentiated SL cells can be delivered to the subject to treat the medical condition.

Stem cells can also be delivered into an individual according to retrograde or antegrade delivery. As an example, cells can be introduced into an organ of an individual via retrograde delivery of the cells into the organ. Non-limiting examples of such organs can include the heart, the liver, a kidney, the brain, pancreas, and the like.

Additionally, in some aspects SL cells can be lysed and the lysate used for treatment. In other aspects, supernatant from the culture process can be used for treatment. One example of such a supernatant treatment includes the delivery of exosomes. Exosomes can be delivered into the individual via aerosolized delivery, IV delivery, or any other effective delivery technique. Exosomes can also be used to treat individuals with open wounds, ulcers, burns, and the like.

In a further aspect, a method of treating COPD is provided. Such a method can include administering a COPD effective active agent intravenously to a patient to deliver the COPD effective active agent to a lower half of the patient's lung, and also administering the COPD effective active agent in an aerosolized form to the patient via ventilation to deliver the COPD effective active agent to an upper half of the patient's lung. In some embodiments, the administration can be concomitant. In other aspects, the administration can be sequential. In some aspects, the COPD effective agent delivered intravenously can be different from the COPD effective agent delivered in aerosol form, while in other aspects the same COPD effective agent can be utilized in both administrations. In some cases it can be beneficial for the patient to be in a sitting position during delivery of the COPD effective active agent. In one aspect, the COPD effective active agent includes stem cells. In another aspect, the stem cells include the cells described herein. In another aspect, the active agent can be a pharmaceutical agent, or a biologic agent. Other non-limiting examples of COPD effective active agents can include exosomes, cell lysates, protein extracts, protein extracts derived from cell culture, and the like.

A variety of conditions can be utilized to aerosolize cells. In one aspect, for example, cells can be suspended in 1-5 mls of saline and aerosolized at a pressure of 3-100 psi for 1-15 minutes, or until the cells begin to rupture and/or die.

Any form of aerosolizer can be utilized to deliver stem cells to the lungs provided the stem cells can be delivered substantially without damage. In some cases, it can be beneficial to aerosol stem cells via an aerosolizer capable of aerosolizing particles to in larger sizes. For example, in one aspect, an aerosolizer can be used that aerosolizes to a particle size of from about 2 microns to about 50 microns. In another aspect, an aerosolizer can be used that aerosolizes to a particle size of from about 4 microns to about 30 microns. In yet another aspect, an aerosolizer can be used that aerosolizes to a particle size of from about 6 microns to about 20 microns. In yet another aspect, an aerosolizer can be used that aerosolizes to a particle size of from about 6 microns to about 200 microns.

In another example, the present techniques can be utilized in the treatment of acute radiation syndrome. Acute radiation syndrome can be challenging to treat, with survival being dependent on the dose of radiation and the subsequent

clinical care to mediate lethal infections, including providing support for resident stem cell expansion. Traditional techniques utilize growth factor treatment or hematopoteitic stem cell transplantation. The stem cells according to aspects of the present disclosure can be used under allogeneic transplant models with no HLA matching needed between donor and host. The cells have been shown to be hypoimmunogenic and not recognized by the immune system, even following multiple injections. These stem cells secrete several bioactive molecules, such as hematopoietic growth factors including IL6, IL11, LIF SCF and Fly3 ligand and immunomodulatory molecules such as TGFB1, prostaglandin E2, indoleamine 2,3-dioxygenase.

Such cultured cells facilitate a protective mechanism combating the inflammatory cascade in addition to supporting detoxification after radiation exposure. In addition, these cells release trophic factors and HSC-niche modulating activity to rescue endogenous hematopoiesis and activity. This data suggest that these cells serve as a fast and effective treatment in a first-line of defense to combat radiation-induced hematopoietic failure. In addition these cells may be used to treat severe or steroid resistant graft vs. host disease.

EXAMPLES

Example 1

Composition for Culturing Cells or Stem Cell from Umbilical Cord for Clinical Use

Media Composition-1
DMEM-Low Glucose—Phenol Free
1× Glutamine
1× NEAA
10% PRP Lysate or platelet lysate
1000 units of heparin
Media Composition-2
DMEM-Low Glucose—Phenol Free
1× Glutamine
1× NEAA
Lyophilized 10% PRP Lysate or platelet lysate Tablet
1000 units of heparin
Media Composition-3
DMEM-Low Glucose—Phenol Free
1× Glutamine
1× NEAA
10% PRP Lysate or platelet lysate
ACD

Example 2

Culturing Cells or Stem Cell from Umbilical Cord for Clinical Use

Umbilical cord tissue is obtained and maternal blood is tested for infectious disease prior to derivation of cell and stem cell populations. A 1 cm piece of cord is washed 10 times in a solution of DPBS containing 10% PRP-Lysate or platelet lysate. The umbilical cord is then opened longitudinally to expose the interior of the umbilical cord. All tissue is removed that can give rise to endothelial cells. The umbilical cord is then place directly into a cell culture dish containing Media Composition-1 with the interior of the umbilical cord in contact with the plastic and cultured in either normoxic or hypoxic culture environments.

On the third day the media is replaced with fresh Media Composition-1 and cultured until day seven when the explants are removed for primary cell expansion. The cells are fed every other day until approximately 500,000-1,000,000 cells can be harvested and further expanded. It is noted that the media used for subsequent examples is Media Composition-1 unless specifically noted otherwise.

Example 3

Enzymatic Passage of Cells or Stem Cell from Umbilical Cord for Clinical Use

TrypLE can be used for subculturing the cells. The media is removed from the flask of Example 2 and the cells are washed three times with DPBS. TrypLE is then added and the cells are transferred to the incubator at 37 C for 3-5 minutes. The enzymatic reaction is stopped by the addition of equal volume of culture/expansion media. The cells are then centrifuged 400×g for 5 minutes at room temperature. The supernatant is removed and the cells are washed 3 times if they will be further subcultured or 10 times if they will be used therapeutically.

Example 4

Non-Enzymatic Passage of Cells or Stem Cell from Umbilical Cord for Clinical Use

For a non-enzymatic approach, a semi-solid gel can be used to remove the cells from the tissue culture flask. The cells are cultured in normal culture/expansion media. One day prior to subculture, freshly prepared DMEM-Low Glucose—Phenol Free, 1× Glutamine, 1× NEAA, 10% PRP Lysate or platelet lysate, ACD semi-solid media is added to the cells. The cells are cultured overnight under either a normoxic or hypoxic environment. The following day a semi-solid gel is formed over the cells. To remove the cells from the dish, the side of the dish is tapped until the semi-solid gel is dislodged from the bottom. This semi-solid layer can then be removed, and the cells will be located within the semi-solid gel. If further subculture is required the semi-solid gel is transferred to additional cell culture flasks or bags for further expansion. If the cells are not to be further expanded the semi-solid layer containing the cells can be directly applied therapeutically.

Example 5

Therapeutic Use of Cells or Stem Cells from Umbilical Cord for Treating Critical Limb Ischemia

Patients qualified for inclusion if they had chronic, critical limb ischemia including rest pain (Rutherford class 4) or mild-to-moderate tissue loss (Rutherford 5) and were not candidates for surgical or endovascular revascularization. Hemodynamic parameters included one of the following: ankle pressure<50 mmHg or ABI<0.4; toe pressure<40 mmHg or TBI<0.4; or TcPO2<20 mmHg on room air.

Exclusion criteria included extensive necrosis of the index limb making amputation inevitable (Rutherford class 6); uncorrected iliac artery occlusion ipsilateral to index limb; lack of Doppler signal in the index limb (ABI=0); serum creatinine≥2.0 mg/dL; active infection requiring antibiotics; active malignancy; or any hematologic disorder that prevented bone marrow harvesting.

All patients were ≥18 years of age and able to provide informed consent. All enrolled patients underwent pre-operative cancer screening and ophthalmologic examinations for proliferative retinopathy.

Cells were produced as described in Examples 1-4. The vascular surgeon made 40 intramuscular injections of 1 mL aliquots of cells or stem cells derived from umbilical cord into previously identified locations along the ischemic limb using ultrasound guidance. Procedures were carried out under local anesthesia and conscious sedation.

Patients were evaluated at 1, 4, 8, 12 and 26 weeks post-procedure. Clinical outcomes included amputation status, Rutherford classification of limb ischemia, and pain as determined by Visual Analog Scale (VAS). Major amputations were defined as those occurring above the ankle Hemodynamic outcome was evaluated by Ankle Brachial Index (ABI). Laboratory monitoring of hematology and blood chemistries was also performed. Ophthalmologic retinal examination was performed at baseline and 12 weeks in diabetics to evaluate for proliferative retinopathy. Results are shown in FIGS. **11**A and **11**B. Injection only represents the delivery of stem cells, while the control was a saline solution lacking the stem cells.

Example 6

Therapeutic Use of Cells or Stem Cells from Umbilical Cord for Treating Chronic Refractory Angina and/or Congestive Heart Failure

Patients with Canadian Cardiovascular Society (CCS) class III-IV angina despite maximal medical or surgical therapy who were ineligible for further percutaneous or surgical revascularization (based on coronary anatomy) and who had evidence for reversible ischemia on an exercise single photon emission computed tomography (SPECT) were enrolled.

Cells were produced as described in Examples 1-4. The femoral vein was cannulated with a 7 French sheath, a 6 French catheter was placed in the coronary sinus and a 0.035 mm hydrophilic guide wire was placed in the interventricular or lateral vein followed by placement of a peripheral balloon into the mid portion of the coronary sinus to allow nonselective delivery of cells. (Cook Medical, Indiana, USA). The balloon was inflated at very low pressure (1 to 2 atm) for 10 minutes producing stagnation of the flow. 50 mls of cells (50,000,000-400,000,000) were injected manually through the balloon at a rate of 10 mls per minute. The average total procedure time for cell delivery was 30 minutes. FIG. **12** shows an angiogram demonstrating delivery of cells into the heart using a retrograde technique.

The baseline screening assessment of patients included clinical evaluation, electrocardiogram (ECG), laboratory evaluation (complete blood count, blood chemistry, erythrocyte sedimentation rate, creatine kinase, and troponin T serum levels). Patients kept a record of daily angina frequency for three weeks, and the severity of angina was graded according to the CCS class at baseline, 3, 12, and 24 months. Within two weeks prior to cell therapy, exercise capacity was evaluated using bicycle ergometry in conjunction with SPECT imaging to assess myocardial ischemia and left ventricular (LV) function.

Example 7

Heart Failure Safety Study

Ten patients, 5 ischemic and 5 non-ischemic, received retrograde delivery of cells to the heart as described in Example 6. FIGS. **13**A-D shows time lapse images of such a retrograde delivery. The baseline screening assessment of patients included clinical evaluation, electrocardiogram (ECG), laboratory evaluation (complete blood count, blood chemistry, erythrocyte sedimentation rate, creatine kinase, and troponin T serum levels). Patients were given follow up assessments at 1, 3, 6, and 12 months. Tables 1 and 2 show results over time for ischemic and non-ischemic patients.

TABLE 1

Ischemic	Baseline	1 month	3 month
Troponin	0.03	0.02	0.02
BNP	543	320	178
EF %	26	33	38
6 m.w.	255	260	344
VO_2 Max	14	15	17
AE/SAE	0/0	1/0	1/0

TABLE 2

Non-Ischemic	Baseline	1 month	3 month
Troponin	0.03	0.03	0.02
BNP	655	389	156
EF %	22	34	39
6 m.w.	227	235	312
VO_2 Max	13	15	19
AE/SAE	0/0	0/0	1/0

Example 8

Therapeutic Use of Cells or Stem Cells from Umbilical Cord for Diabetes

Cells are produced as described in Examples 1-45. Therapeutic doses can be 50,000,000-400,000,000. The cells are delivered thru arterial access into the celiac and or SMA artery, thereby delivering cells into the head and/or tail of the pancreas via infusion technique.

Example 9

Therapeutic Use of Cells or Stem Cells from Umbilical Cord for Treating COPD/Asthma/Emphysema

The following inclusion criteria were used for subjects in this study. Individuals were included having:

- moderate or severe COPD with a post-bronchodilator FEV1/FVC ratio <0.7
- subject must have a post-bronchodilator FEV1% predicted value >30%
- current or ex-smoker, with a cigarette smoking history of >20 pack-years

Subjects exhibiting one or more of the following were excluded from the study:

- diagnosed with asthma or other clinically relevant lung disease other than COPD (e.g. restrictive lung diseases, sarcoidosis, tuberculosis, idiopathic pulmonary fibrosis, bronchiectasis, or lung cancer)
- diagnosed with α1-Antitrypsin deficiency
- body mass greater than 150 kg or less than 40 kg
- subject has an active infection
- subject has had a significant exacerbation of COPD or has required mechanical ventilation within 4 weeks of screening

uncontrolled heart failure, atrial fibrillation

cardiopulmonary rehabilitation initiated within 3 months of screening

subject has evidence of active malignancy, or prior history of active malignancy that has not been in remission for at least 5 years

subject has a life expectancy of <6 months

Cells are produced as described in Examples 1-4. Therapeutic doses can be 50,000,000-400,000,000 cells. While a subject is sitting upright the cells are administered simultaneously thru an aerosolized delivery which will remain top half of the lung due to normal physiologic ventilation perfusion and is given intravenous which is delivered to the lower half of the lung, due to the natural ventilation perfusion for a person sitting upright. This combined technique is used due to the fact that either one performed alone does not deliver sufficient biologic to the entire lung volume.

20 test subjects were divided into 4 groups and received the following:

5 subjects in Group 1 were given placebo—saline injection

5 subjects in Group 2 were given IV delivery—200M cells

5 subjects in Group 3 were given inhaled delivery—200M cells

5 subjects in Group 4 were given IV and inhaled delivery—100M/100M cells

Results obtained from these groups treated with no cells, IV only, inhaled only and both IV and inhaled are shown in Table 3.

Regarding aerosolization, cells were prepared as described, suspended in 1-5 mls of saline and aerosolized at a pressure of 30 psi for 8-10 minutes

TABLE 3

	Placebo Group 1	IV Group 2	Inhaled Group 3	IV and Inhaled Group 4
FEV1/FVC pre	0.55 ± 0.15	0.49 ± 0.08	0.51 ± 0.10	0.47 ± 0.07
FEV1/FVC post	0.52 ± 0.13	0.53 ± 0.12	0.57 ± 0.11	0.66 ± 0.05
O_2L/min pre	3.0 ± 1.0	2.8 ± 1.2	3.2 ± 1.0	2.8 ± 1.2
O_2L/min post	3.2 ± 1.2	2.4 ± 1.4	2.5 ± 1.2	2.0 ± 1.0
MAP/CE	2	0	0	0

Example 10

Therapeutic Use of Cells or Stem Cells from Umbilical Cord for Treating Wound Healing

Cells are produced as described in Examples 1-4. Therapeutic doses can be 50,000,000-400,000,000 cells in this example. Cells are delivered to the wound via injection and/or aerosolized in a PL-carrier with addition of liquid calcium and thrombin.

Example 11

Therapeutic Use of Cells or Stem Cells from Umbilical Cord for Orthopedic Applications

Cells are produced as described in Examples 1-4. Therapeutic doses can be 50,000,000-400,000,000 cells in this example. Under ultrasound guidance the cells are directly injected into the intraarticular space/joint with or without a micro fracture technique. They cells may also be delivered with PRPL or PL carrier in addition to liquid calcium/thrombin. As one example, FIGS. **14**A and **14**B show images of the knee of an 80 year old female prior to the delivery procedure. FIGS. **14**C and **14**D show images of the same knee from the same 80 year old female 3 months post-transplant. It is noted that more intraarticular space is observed in the patient in the post-transplant images.

Example 12

Therapeutic Use of Cells or Stem Cells from Umbilical Cord for Acute Radiation Syndrome Applications in Mice

Female C57BL/6J mice were used as the recipient population. Umbilical cord stem cells were isolated as previously described but isolated in this case from mice. The female C57BL/6J mice received TBI using a Cs-137 radiation source. Lethal irradiation was performed using 9.5 Gy. Within 8 hours post irradiation mice received transplants intravenously. Evaluation of peripheral blood counts of animals treated with stem cells revealed similar leukocyte and thrombocyte recovery as observed in recipients treated with HSCs. (See FIGS. **15**A-B) Seven months post transplantation recipients were hematologically well with a normal distribution of peripheral blood cell populations. (See Table 4).

TABLE 4

Peripheral blood cell population in transplanted mice

lymphocytes	neutrophils	monocytes	eosinophils
72% +/− 3	21% +/− 3	5% +/− 2	2% +/− 1

Example 13

Therapeutic Use of Cells or Stem Cells from Umbilical Cord for Acute Radiation Syndrome Applications in Humans

In order to determine if human derived subepithelial layer umbilical cord cells had the same effect as Example 12, the same experiment was repeated using human-derived cells as the donor material and nod/scid gamma(c) null mice as the recipient. Animals were treated as previously described and transplanted IV at 6, 12 and 24 hours post total body irradiation (TBI). 6 months post transplant all (n=30) control mice that didn't receive cells post TBI were dead. FIG. **16** shows the survival of mice receiving human cells 6, 12 and 24 hours post TBI.

Of course, it is to be understood that the above-described arrangements are only illustrative of the application of the principles of the present disclosure. Numerous modifications and alternative arrangements may be devised by those skilled in the art without departing from the spirit and scope of the present disclosure and the appended claims are intended to cover such modifications and arrangements. Thus, while the present disclosure has been described above with particularity and detail in connection with what is presently deemed to be the most practical embodiments of the disclosure, it will be apparent to those of ordinary skill in the art that numerous modifications, including, but not limited to, variations in size, materials, shape, form, function

and manner of operation, assembly and use may be made without departing from the principles and concepts set forth herein.

What is claimed is:

1. An isolated cell prepared by a process comprising:

placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate; and

culturing the subepithelial layer such that the isolated cell from the subepithelial layer is capable of self-renewal and culture expansion,

wherein the isolated cell expresses at least three cell markers selected from the group consisting of CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, or CD105, and

wherein the isolated cell does not express NANOG and at least five cell markers selected from the group consisting of CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, or HLA-DR.

2. The isolated cell of claim **1**, wherein the isolated cell expresses CD29, CD73, CD90, CD166, SSEA4, CD9, CD44, CD146, and CD105.

3. The isolated cell of claim **1**, wherein the isolated cell does not express CD45, CD34, CD14, CD79, CD106, CD86, CD80, CD19, CD117, Stro-1, and HLA-DR.

4. The isolated cell of claim **1**, wherein the isolated cell is positive for SOX2.

5. The isolated cell of claim **1**, wherein the isolated cell is positive for OCT4.

6. The isolated cell of claim **1**, wherein the isolated cell is positive for SOX2 and OCT4.

7. The isolated cell of claim **1**, wherein the wherein the isolated cell is capable of differentiation into a cell type selected from the group consisting of adipocytes, chondrocytes, osteocytes, cardiomyocytes, endothelial cells, and myocytes.

8. The isolated cell of claim **1**, wherein the isolated cell produces exosomes expressing CD63, CD9, or CD63 and CD9.

9. The isolated cell of claim **1**, wherein culturing comprises culturing in a culture media that is free of animal components.

10. A culture of differentiated cells derived from the isolated cell of claim **1**, wherein the culture of differentiated cells includes a cell type selected from the group consisting of adipocytes, chondrocytes, osteocytes, cardiomyocytes, endothelial cells, myocytes and combinations thereof.

11. The isolated cell of claim **1** that has been differentiated into an adipocyte cell.

12. The isolated cell of claim **1** that has been differentiated into a chondrocyte cell.

13. The isolated cell of claim **1** that has been differentiated into an osteocyte cell.

14. The isolated cell of claim **1** that has been differentiated into a cardiomyocyte cell.

15. The isolated cell of claim **1** that has been expanded into a cell culture.

* * * * *

FORM 19. Certificate of Compliance with Type-Volume Limitations **Form 19**
July 2020

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS

Case Number: 2023-2054

Short Case Caption: Restem, LLC v. Jadi Cell, LLC

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Name: Kevin C. Hooper