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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.

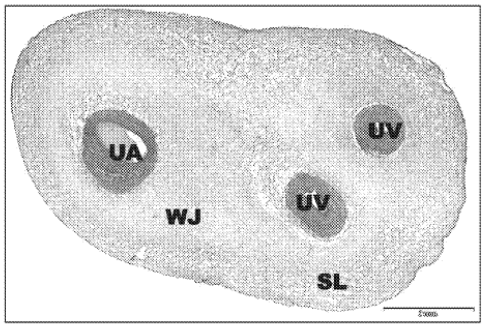

FIG. 1

[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:

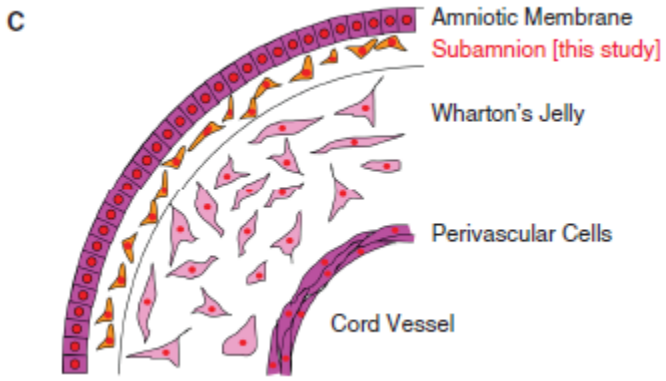

Figure 1 C is a "[d]iagram of the origin of cord lining membrane (CL)-mesenchymal stem cells (MSCs)." *Id.* at 493.

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.