23-2054

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

RESTEM, LLC,

Appellant,

—v.—

JADI CELL, LLC,

Appellee.

ON APPEAL FROM THE UNITED STATES PATENT AND TRADEMARK OFFICE
IPR2021-01535

CORRECTED BRIEF FOR APPELLEE

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UNITED STATES PATENT NO. 9,803,176

CLAIM 1

1. An isolated cell prepared by a process comprising:

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

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

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

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

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 23-2054

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

Filing Party/Entity Jadi Cell, LLC

Instructions:

1. Complete each section of the form and select none or N/A if appropriate.
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5. Counsel must file an amended Certificate of Interest within seven days after any information on this form changes. Fed. Cir. R. 47.4(c).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 07/06/2023

Signature: /s/ Jed Hansen

Name: Jed Hansen

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

☐ Additional pages attached

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

☑ None/Not Applicable ☐ Additional pages attached

5. Related Cases. Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

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

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

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

☑ None/Not Applicable ☐ Additional pages attached

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TABLE OF AUTHORITIES

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TABLE OF ABBREVIATIONS

Term	Abbreviation
Jadi Cell, LLC	Jadi Cell
Restem, LLC	Restem
Umbilical Cord	UC
Subepithelial Layer	SL
Wharton's Jelly	WJ
Stem Cell	SC
Mesenchymal Stem Cell	MSC
International Society for Cell & Gene Therapy	ISCT
Final Written Decision	FWD
United States Patent Office, Patent Trial and Appeal Board	Board
Person of Ordinary Skill in the Art	POSITA

STATEMENT OF RELATED CASES

Counsel for Appellee Jadi Cell, LLC ("Jadi Cell") is unaware of any related cases within the meaning of Federal Circuit Rule 47.5.

JURISDICTIONAL STATEMENT

The United States Patent Office, Patent Trial and Appeal Board ("Board") had jurisdiction over the inter partes review that is the subject of this appeal under 35 U.S.C. § 6. The Board issued a Final Written Decision ("FWD") on April 18, 2023 on the inter partes review pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Appellant Restem, LLC ("Restem") filed a Notice of Appeal of the FWD on June 16, 2023. This Court has jurisdiction of the appeal under 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C § 141(c).

STATEMENT OF THE ISSUES

1. Whether the Board's implicit construction of "isolated cell" as part of its construction of "expressed/not expressed" is supported by substantial evidence or constitutes harmless error.

2. Whether substantial evidence supports the Board's finding that Restem failed to demonstrate by a preponderance of the evidence that claims 1-15 of U.S. Patent No. 8,803,176 were unpatentable pursuant to 35 U.S.C. § 102 or claim 9 was unpatentable pursuant to 35 U.S.C. § 103.

STATEMENT OF THE CASE

The challenged claims of U.S. Patent 9,803,176 (the "'176 Patent") concern a product-by-process claim. The claimed product is an isolated cell population having specific cell markers (the "Claimed Cells"). Not a single prior art reference discloses cells having the claimed cell markers. The two process steps that make up the product-by-process claim were construed broadly. The Board found that the prior art discloses the process steps, but the prior art does not disclose or render obvious the Claimed Cells. As such, the challenged claims are not unpatentable. Restem contends that because the prior art discloses the broadly construed process steps, it must inherently disclose the Claimed Cells. As explained in greater detail below, these arguments are wrong based on both the facts and the law.

The Board instituted inter partes review under the lower "reasonable likelihood of success" standard, initially crediting testimony from Restem's expert. At the close of trial, and after a careful review of trial testimony from all expert and fact witnesses, extensive briefing, and oral argument, the Board issued an exhaustive 75-page opinion and

order articulating why the prior art cited by Restem did not render any of the claims of the '176 Patent unpatentable. That opinion and order should be affirmed.

On appeal, Restem criticizes the Board on three primary grounds. First, Restem criticizes the Board for "implicitly" construing the term "isolated cell" to mean "a population of cells isolated from tissue." Appellant's Br. 48. More specifically, Restem argues that while the Board did not expressly construe the term "isolated cell" in the FWD, the Board determined that the term "express/does not express" implicitly requires "an isolated cell" to mean an isolated population of cells. *Id.* Restem argues that the Board's implicit construction of "isolated cell" "ignores the express definitions of the '176 patent." *Id.*

Restem's criticisms lack merit. Construction of "express/does not express," which included a tangential reference to "isolated cell" as a "cell population," is supported by substantial evidence of a POSITA's understanding of those terms. That understanding is premised on an analysis of the specification, the surrounding claim terms, relevant prosecution history, and expert testimony. Appx25–28. That said, even

if the Board's reference to an "isolated cell" as a "cell population" is not supported by substantial evidence, Restem has not shown that it was prejudicial error. Indeed, the Board did not rely on the meaning of the term "isolated cell" in making its final determination that the prior art failed to anticipate or render obvious any of the challenged claims.

Second, Restem essentially argues that the Board should adopt a new legal standard. The Board found, and no party disputes, that the claims at-issue are product-by-process claims. The Board properly cited to and relied on this Court's precedent involving product-by-process claims. Namely, that "[i]n determining validity of a product-by-process claim, the focus is on the product and not the process of making it." *Kamstrup A/S v. Axioma Metering UAB*, 43 F.4th 1374, 1381 (Fed. Cir. 2022) (quoting *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012)); *see also* Appellant's Br. 51. Restem faults the Board for following this well-established precedent. More specifically, Restem argues that once the Board found that the prior art disclosed the recited process steps of claim 1, the Board's patentability analysis was over, and the claimed product must be anticipated or obvious as a

matter of law. Restem's legal theory runs contrary to years of well-established law and conflates the function of the patent claims with the patent specification.

Third, Restem accuses the Board of implicitly reading additional "placing steps" and other "factors" and "conditions" into the claimed process steps. The Board did no such thing. The challenged claims recite cells with a specific gene marker expression profile. Broadly speaking, the '176 Patent teaches that the Claimed Cells, specifically the recited gene marker profile, can be derived from culturing the subepithelial layer (SL) from mammalian umbilical cord ("UC"). In one embodiment, the UC is opened and Wharton's Jelly (WJ) and other tissues are removed from the SL. The SL is then placed directly on a growth medium for culturing. Appx94 at 2:9–28. Jadi Cell argued for a narrow construction of process steps that would include these limitations. Appx19–21.

The Board, however, construed the process steps of the challenged claims broadly, consistent with Restem's proposed construction. Appx17–24. Due, at least in part to that breadth, the Board concluded

that based on the factual record, following the broadly construed process steps would not necessarily result in the marker expression profile of the Claimed Cells. Appx42 ("We recognize that the process steps of claim 1 are quite broad when construed in light of the patent…").

Explaining its rational (i.e., why following the broadly construed process steps would not necessarily yield the Claimed Cells), the Board referenced a variety of different specific process steps that could be employed that would change the gene marker expression of the isolated cell population. Appx40–42. The Board also cited undisputed record evidence of various "factors" and "conditions" affecting all cell cultures. *Id*. The Board cited this evidence as additional support for why the broadly construed process steps would not necessarily or obviously yield the Claimed Cells.

That said, the Board's recitation of those steps, factors, or conditions are not "limitations" read into the claims. Rather, they are facts that support the Board's conclusion that the broadly construed process steps recited in the challenged claims can, and do, yield a

variety of unpredictable combinations of gene markers—none of which are necessarily or obviously the gene markers of the Claimed Cells. Appx42–43.

In sum, the Board found that the process steps (broadly construed) were disclosed in the prior art. Appx39. The Board also found that those steps did not necessarily result in the Claimed Cells (Appx40) and that the prior art did not directly disclose the Claimed Cells. Appx37–38. Because the prior art does not directly or inherently disclose the Claimed Cells, the prior art neither anticipates nor obviates the challenged claims. Appx76.

STATEMENT OF FACTS

A. THE '176 PATENT

Jadi Cell is the owner of the '176 Patent. Driven by a desire to find a cure for his son's autoimmune disorder, Dr. Amit Patel, the inventor of the '176 Patent, conducted several years of research that ultimately led to the filing of Application No. 13/732,204. Appx3353, ¶¶13–15. The '176 patent, titled "Methods and Compositions for the Clinical Derivation of an Allogenic Cell and Therapeutic Uses" was

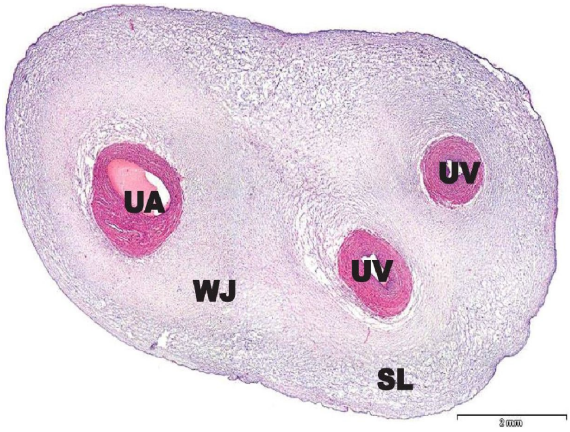
issued on October 31, 2017, from that application. Appx78. That application was filed August 22, 2013. *Id.*

The '176 Patent discloses "an allogenic cell or stem cell population that can be used for treating a wide range of conditions"[1] and the specification teaches the POSITA methods of "isolating, culturing, developing, or otherwise producing these cells." Appx3–4. An allogenic cell is one that is "genetically different although belonging to or obtained from the same species." Appx4. Stem cells are cells with "the ability to differentiate along different lineages and the ability to self-renew." *Id.* "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

[1] Non-invasive treatments for ARDS patients, for example, are elusive. *See generally,* Appx3362, ¶42. The Claimed Cells are a hopeful resolution to that problem. A randomized double-blind study showed that treatment of ARDS patients with the Claimed Cells had a much lower mortality rate than a control group. *See* Appx3050-3052, ¶¶17–22. Several companies license the '176 Patent to harvest cells for different beneficial applications (*See* Appx3358-3361, ¶¶30–40) and a Phase III clinical trial of the Claimed Cells has been approved by the FDA. Appx3359-3360, ¶¶36–37.

umbilical cord, endometrial polyps, menses blood, bone marrow, adipose tissue, etc." *Id.*

Mammalian umbilical cord ("UC") tissue is the subject of the Claimed Cells. A cross-section of UC is provided as FIG. 1 of the '176 Patent:



Appx80, Fig. 1.

Generally speaking, the UC is composed of four structures. These are, from outermost to innermost:

a. The amniotic membrane (also known as the amniotic epithelium);

b. The subepithelial layer (also known as the subepithelium);

c. Wharton's Jelly; and

d. UC blood vessels.

Appx3639, ¶45.

The specification teaches the POSITA that the target stem cell population is obtained from the subepithelial layer (SL) of a mammalian UC. After extraction, the cells of the SL are placed on a substrate. Appx4. The SL is then "cultured in a suitable medium . . . for a period of time sufficient to establish primary cell cultures." Appx5. The SL tissue is then removed and discarded, and the cells are further cultured and expanded. *Id.*

The Board cited example 2 of the '176 patent as one method of cell extraction and culturing:

> 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. Appx5.

Put plainly, in one aspect of the technology, the UC is opened and Wharton's Jelly ("WJ") and blood vessels are removed, exposing the SL. That SL tissue is then intentionally placed on the culture media. No other tissue from the UC is mixed in with the culture. Appx5.

Discussed further herein, the Board noted that cells prepared using the process limitations claimed in the '176 Patent would not all have the exact same marker expression profile. Appx40. This is because the '176 Patent discloses numerous examples and different processes associated with the disclosed technology.

B. THE CLAIMED CELLS

While the specification of the '176 Patent teaches the POSITA how to make and use the invention, the claims of the '176 Patent define the scope of that invention. The '176 Patent discloses that cells isolated from the SL tissue "can have a variety of characteristic markers that distinguish them from cell[s] previously isolated from umbilical cord samples." Appx97 at 7:65–67. 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." Appx6 n.4.

The Claimed Cells are isolated from SL tissue of the UC and are disclosed as having certain genetic characteristics, as defined by their cell markers. Among other characteristics, 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." Appx98 at 9:53–60. Positive NANOG expression is not only a desired characteristic of stem cells but is noted in the art as a "key molecule[] necessary for the maintenance of self-renewal of SCs." Appx1923. As such, negative NANOG expression is an unexpected characteristic of prior art MSCs. Appx3811, ¶ 26.

Claim 1 is the only independent claim of the '176 Patent and is representative of the core issues on appeal.

[Pre]	An isolated cell prepared by a process comprising:
[A]	placing a subepithelial layer of a mammalian umbilical cord tissue in direct contact with a growth substrate; and
[B]	culturing the subepithelial layer such that the isolated cell from the subepithelial layer is capable of self-renewal and culture expansion,
[C]	wherein the isolated cell does not express NANOG;
[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;
[E]	wherein the isolated cell does not express…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 4-6 are also relevant to the appeal and are noted below.

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

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

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

C. Overview of Select Prior Art

After an exhaustive review, the Board found that Restem failed to prove that the Claimed Cells were anticipated or obvious in view of the

prior art. Prior art relevant to this appeal is summarized below. Importantly, however, there is no dispute that none of the prior art discloses any cells which are positive for SOX2 and OCT4, are negative for NANOG, and positive for CD44, CD90 and CD146, for example. Equally important, no prior art discusses any facts that a POSITA would find helpful or useful in culturing cells with the exact marker profile of the Claimed Cells.

1. Majore

Majore focuses on the growth and differentiation properties of mesenchymal stromal cells that are derived from whole human UC tissue. In other words, Majore derives cells from all the components of the human UC mixed together. As noted by the Board, "Majore uses the word 'subepithelial' only once to explain that primitive stem cells are 'distributed in subepithelial and intervascular regions.'" Appx52. Majore notes "[a]t the laboratory UC was 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… After 2 weeks, the tissue pieces were removed and the adherent cells were harvested." Appx29–30.

Majore discloses that surface markers CD34, CD73, CD90, and CD105 were detected in the cells (Appx30) and that the studied cells do not express only two surface markers, CD34 and CD45. Appx38, Table 2. Majore is silent as to the non-expression of the other claimed non-expressed surface markers and silent as to the expression or non-expression of NANOG. *Id*. No party disputes that this does not comprise the Claimed Cells.

Restem's expert testified that his lab "routinely" uses the Majore protocol (as often as three times a week) to handle UC tissue. Appx4149–4150 at 61:21–63:12. Despite this alleged frequency, Restem failed to submit any evidence that the cells resulting from the Majore process were the same as the Claimed Cells. Appx4150–4151 at 62:20–63:2. Indeed, neither Restem's expert nor his lab has ever tested any Majore-protocol cells, including testing for NANOG. Appx4150 at 63:13–19.

Restem also argued at trial that the Claimed Cells were obvious in view of Majore because certain of the recited markers were consistent with International Society for Cell & Gene Therapy ("ISCT") criteria for MSCs. Appx49–50. However, among other differences, Majore's cells did not differentiate under standard *in vitro* conditions, one of the ISCT's criteria for MSCs. *See* Appx3681, ¶ 152; Appx1942.

2. Phan

Phan discloses a method for isolating stem/progenitor cells from the amniotic membrane of the UC that separates "the amniotic membrane from the other components of the umbilical cord *in vitro*, culturing the amniotic membrane tissue under conditions allowing cell proliferation, and isolating the stem/progenitor cells from the tissue cultures." Appx2168, ¶ 1. Phan discloses an embodiment to isolate "epithelial and/or mesenchymal stem/progenitor cells." Appx2178, ¶ 43. Phan does not isolate cells solely from the subepithelial layer of the UC. Appx3664, ¶ 109.

Restem acknowledges that Phan does not disclose the Claimed Cells because it "is silent as to the 'at least three' expressed markers,"

"silent as to the 'at least five' non-expressed markers recited in [claim 1]," and also "silent as to the expression of SOX-2." Appx251, 254. The cells from Phan "expressed 140 genes related to embryonic stem cells and embryonic development . . . **[including] Nanog.**" Appx2192, ¶ 88. (emphasis added). Contrary to the Claimed Cells, which do not express NANOG, Phan notes that the positive expression of NANOG is "related to embryonic stem cells and embryonic development," and further noted that its MSCs "have embryonic stem cell-like properties." *Id*.

3. Kita

Kita discloses a protocol to "isolate adult [stem cells] from the cord lining membrane (subamniotic region of the umbilical cord), and characterize the isolated cells as a novel source for cell-based therapeutic approaches." Appx1920. Human UC was washed and cut into 1-inch pieces and dissected to open the cord, then placed in petri dishes with growth medium and incubated. *Id.* Kita does not isolate cells solely from the SL of the UC. Appx3665, ¶¶ 111–112.

Kita is silent as to the non-expression of the "at least five" of the cell markers relevant to Claimed Cells (Appx69) and reports the non-

expression of SOX2. Appx1926. Importantly, contrary to the non-expression of NANOG required by the Claimed Cells, Kita remarks it is "**noteworthy that 100% of cells expressed NANOG, which is one of the key molecules necessary for the maintenance of self renewal of SCs**," and "[t]he other anti-Nanog Ab also showed that all cells in the field of view were Nanog positive[.]" Appx1923 (emphasis added).

4. Pierantozzi

Pierantozzi examined MSCs from human bone marrow, adipose, and cardiac tissues. Pierantozzi did not analyze any UC tissue. Appx1947–1948. Pierantozzi compared the expression of genetic markers in freshly isolated MSCs with the expression of MCSs grown to 80% confluence. Appx1948–1949.

Pierantozzi evaluated "OCT-4, SOX-2…in MSCs by polymerase chain reaction (PCR)," concluding that "[e]xpression of OCT-4 and SOX-2 was not detected by both PCR and immunofluorescence experiments[.]" Appx1947. Pierantozzi also notes:

> A careful investigation performed by immunostaining on consecutive passages of MSCs from bone marrow, adipose, and cardiac tissues revealed that **in all the MSC populations analyzed NANOG was always expressed** in the nuclei of a variable fraction of cells. As shown in fig. 3C, the mean percentage of NANOG-positive cells did not significantly differ between early passages of MSCs from the 3 tissues, although the percentage of NANOG-expressing cells varied up to 5-fold among different MSC preparations even isolated from the same tissue. Appx1949–1950 (emphasis added).

Additionally, Pierantozzi reports that the "percentage of cells expressing NANOG was maintained throughout early passages of MSCs" (Appx1946) and that "[a]ll MSC populations displayed a similar growth rate until p9." *See* Appx1949 ("Since senescent cells were only detected in MSC cultures after p10, we will refer to p1 to p9 as early passages and to p10 to p22 as late passages….").

5. Rojewski

Rojewski is a review article combining observations from over 70 publications about marker expression in numerous different tissues. Appx1970–1971, Table 1. Rojewski does not disclose the Claimed Cells. Most of Rojewski's observations are summarized in Table 1, a sample of which is as follows:

Marker	Synonym	Tissue	Expression	Reference
CD140a	PDGFRα	BM	+	[38]
CD140b	PDGFRβ	BM	+	[40]
		ENDO	+	[58]
CD144	Cadherin-5	BM	–	[6, 38, 61]
CD146	MCAM	BM	+	[7, 42]
		ENDO	+	[58]
		AT	+	[55]

BM = Bone marrow; mPB = G-CSF mobilized peripheral blood; FB = fetal blood; CB = cord blood; PLA = placenta; AM amniotic membrane; CM = chorionic membrane; CV = chorionic villi; ENDO = endometrium; ATSVF = adipose tissue stromal vascular fraction, AT = adipose tissue; PMSC = pancreas mesenchymal stem cells; DPSC = dental pulp stem cells; [a]Detection by real time PCR.

The Rojewski data was derived from MSCs grown from many different tissue types, donors, isolation and culture techniques, and marker expression testing. *Id*. It does not represent any characterization of a particular population of cells.

The Board cited Rojewski's discussion of "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. . . Age and sex of MSC donors may play an important role. . . . Senescence may play an important role during expansion of MSC for clinical purposes… 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). . ..." Appx44.

Rojewski also notes that "[i]t 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 . . . 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." Appx1974, 1978.

With all of the different factors affecting surface marker expression in mind, Rojewski concludes that:

> All things considered, 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.**

Appx41–42, 1980. (emphasis added).

6. Riekstina

Riekstina does not disclose the Claimed Cells. Rather, it focuses on MSCs derived from bone marrow, adipose tissue, dermis, hair follicles, heart, liver, spleen, and dental pulp. Riekstina further notes:

> 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.

Appx1963. (emphasis added).

7. Meiron

Meiron also does not disclose the Claimed Cells. Meiron 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." Appx2051 at 1:6–9.

> "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 1:20–23. (emphasis added).

Meiron analyzed the expression markers for cells from different tissues. Based on the analysis, Meiron discloses the following general information:

> 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-, HLA-DR-, and FMC7-. Other stromal stem cell markers include but are not limited to tyrosine hydroxylase, nestin and H-NF. *Id.* at 20:24–28.

Meiron did not test any umbilical cord tissue.

D. Inventor Evidence Submitted During Prosecution of Patent Describing Testing of Cells

Majore was not cited during prosecution of the '176 Patent, However, during prosecution of the '176 Patent, the inventor submitted evidence demonstrating that the prior art processes, similar to Majore, yields a population of cells that are significantly different from the Claimed Cells. The Examiner initially asserted that the Claimed Cells were "not significantly different from naturally occurring, isolated cells." Appx941, ¶3. To rebut this claim, the inventor submitted test

data to the Patent Office. In these tests, the control cells were isolated following a protocol similar to Majore (i.e., dissected, minced, and digested). *Id.*, ¶5. In contrast to the Majore-like protocol, the Claimed Cells were "washed to remove blood, Wharton's Jelly, and other material associated with the subepithelial layer." *Id.*, ¶6. "Umbilical cord tissue was placed interior side down such that the subepithelial layer was in contact with the growth substrate." *Id.*

The test data was submitted to the Patent Office as proof that "the claimed cells have a distinct gene expression profile [and] … cellular function … as compared to control cells isolated … using conventional isolation techniques." Appx944, ¶ 11. After reviewing this evidence, the Examiner concluded that the data "establishes that the methods for isolating the claimed population produce a markedly different cell population than that of the other methodologies." Appx909, ¶ 5. "In other words, **the methods of isolation cause different phenotypic and genotypic changes in the resultant cell populations**." *Id.* (emphasis added).

Restem asserts that the testing data submitted to the Patent Office during examination was raised for the first time at trial on Reply. Appellant's Br. 18. This assertion lacks merit. Restem itself addressed the test data in its Petition. Appx217. The testing was also addressed in Patent Owner's Preliminary Response (Appx348), and Patent Owner's Response. Appx527, 535 n.17. Trial testimony regarding the testing was provided by Dr. Patel (Appx3354–3356, ¶¶17-25) as well as Jadi Cell's expert. Appx3642–3644, 3678. Importantly, and as noted above, Restem criticizes this data, but offered no contradictory data of its own.

In the FWD, the Board acknowledged Restem's "critique of this testing." Appx43. Noting the absence of any test data from Restem to the contrary, however, the Board concluded that "even if not a perfect comparison to the method of Majore, [it] is at least some evidence that use of a different process to create an isolated cell can result in a different marker expression profile." *Id.*

E. RELEVANT PROCEDURAL HISTORY

Restem filed a Petition pursuant to 35 U.S.C. §§ 311–319 requesting an *inter partes* review (IPR) of claims 1–15 ("challenged claims") of the '176 patent. Appx2. Restem's petition alleged that all but claim 14[2] of the challenged claims were inherently anticipated by Majore or, in the alternative, were obvious in view of Majore, Phan, or Kita in combination with Pierantozzi, Meiron, Riekstina, and Rojewski. Appx377–378.

Jadi Cell filed a Patent Owner Preliminary Response. Appx290. Based on the record before the Board at the time, and applying the lower standard that governs the initial stages of IPRs, the Board instituted trial with respect to the challenged claims on all grounds (Appx2), crediting the initial testimony of Restem's expert (Appx392, 406, 411) and inviting the parties to explore several different areas of interest during trial. Appx392 n.16, 406, 411.

[2] Claim 14 is not relevant to the appeal.

In its institution decision, the Board noted that "to the extent Majore is found at trial not to anticipate but rather only to disclose [less than all of the product claim elements], we advise the parties that we presently view Patent Owner's characterization of evidence of the teachings of Rojewski, Pierantozzi, Meiron, and Riekstina to be more accurate." Appx401; *See also*, Appx407 and Appx413 (giving the same admonition regarding Restem's proposed combination of prior art with Phan and Kita, respectively). Meaning, at the early stages of the proceeding, applying the lighter standard used in institution decisions, the Board was willing to give Restem's expert the benefit of the doubt with respect to certain anticipation arguments, but not to Restem's obviousness challenges.

After institution of trial, Jadi Cell filed a Response, Restem filed a Reply, and Jadi Cell filed a Sur-reply. Appx2. The Board heard oral argument on February 10, 2023 and issued a Final Written Decision on April 18, 2023. Appx1. Restem did not ask for a rehearing or seek leave to file a Sur-reply.

At trial, aside from rebuttal arguments, Restem adduced no new evidence addressing the Board's designated areas of exploration. Following trial, when the Board was no longer required to view the record in a light favorable to Restem, it carefully examined the prior art and witness testimony. On a more complete record, the Board credited Jadi Cell's expert and gave Restem's expert testimony "little weight." Appx52, 63. After weighing the evidence, the Board concluded that Restem had failed to carry its burden of proof. Relevant portions of that analysis and record evidence are noted below.[3]

1. Substantial Evidence Supports the Board's Factual Findings Regarding Claim Construction.

At trial, the Parties proposed different constructions for numerous different claim terms. Appx17. The Board determined that only two phrases required construction in order to make a final determination of

[3] The Board invited the parties to explore different issues at trial including, for example, how to treat negative limitations in the claims. Any of those issues that were not raised on appeal are not addressed herein.

patentability: (1) "placing a subepithelial layer…in direct contact with a growth substrate" and (2) "express/does not express." *Id.*

Jadi Cell proposed that the process step of "placing a subepithelial layer…in direct contact with a growth substrate," should be construed as requiring the removal of Wharton's Jelly ("WJ") from the subepithelial layer of the umbilical cord and placing the exposed subepithelial layer face down directly in contact with a growth substrate. Appx18–19. In contrast, Restem proposed that the phrase means "direct contact with any material capable of being used to obtain explants." Appx18.

The Board opined that the phrase should be read broader than Jadi Cell's proposal, at least in part because the specification did not uniformly require isolation of the subepithelial layer from the UC or removal of WJ prior to the placing step. Appx20. Ultimately, the Board interpreted the phrase to mean "to intentionally place umbilical cord tissue comprising the subepithelial layer so that it touches a growth substrate to permit cell culture." *Id.* Restem does not dispute the Board's construction of this phrase.

With respect to the terms "express/do not express," Restem proposed that the terms mean the recited gene marker is detected above the level of a negative control. Appx25. Jadi Cell proposed that the terms be construed to mean the recited gene marker is (or is not, respectively) detected above the level of a negative control in a significantly high percentage of the isolated cells tested. *Id*.

The Patent Examiner understood that the challenged claims were directed to a population of cells. At the very beginning of the examination process, the Examiner issued a restriction requirement regarding claims "drawn to a cell population." Appx1342. During prosecution, the Examiner referred to "isolated cell" as "applicant's claimed cell population" (Appx1227), and reiterated that "the claims only contain limitations to a population of cells." Appx1006. The Examiner's reason for allowance leaves no doubt that the POSITA understood the claims to be directed to a cell population.

> Applicant's submission of an affidavit by Dr. Amit Patel dated 6/21/17 establishes that the methods of isolating **the claimed population** produce a markedly different **cell population** than that of the other methodologies. In other words, the methods of isolation cause different phenotypic and genotypic

> changes in the resultant **cell populations**. For at least this reason, and the reasons evident in the prosecution history, the present claims are found to be allowable.

Appx909 (emphasis added). Claim language also makes clear that the "isolated cell" that is found in the "subepithelial layer" must be "capable of self-renewal and culture expansion," thereby creating a population of cells. Appx103.

Consistent with the prosecution history, Jadi Cell explained that the term "expression" must be read in the context of "isolated cell," "culturing," and "self-renewal and culture expansion." Appx3638–3641, ¶¶ 43-48; Appx3656–3658, ¶¶ 88–94. Reading the claim as a whole to refer only to a single cell with the claimed characteristics, would render "express" or "does not express" meaningless. *See* Appx3658, ¶ 94.

At trial, Restem disputed that Jadi Cell's construction that "express/does not express" must refer to a population of cells. Appx25–26. Ironically, counsel for Restem admitted during oral argument that it was not "a technical possibility" to look at every marker simultaneously on a single cell. Appx832–833 at 11:25–12:2. Moreover, during trial, Restem's expert consistently referred to the Claimed Cells

as a population of cells. *See* Appx1717, ¶54 (testifying about "purported 'novelty' of… a stem cell population…"); Appx1723, ¶ 54; Appx1724 ¶ 64 (where "evidence of differences in gene expression and in ability to differentiate between a population of umbilical cord cells … ["control cells"] and a population of umbilical cord cells obtained by an explant procedure."); Appx1724 ¶ 65. ("selected and expanded population of MSCs was used as the 'Claimed Cells.…") (emphasis in original); Appx1718, ¶ 56 ("POSITA would understand that there is heterogeneity of MSC populations..."); Appx1743, ¶ 93 ("Majore's process of isolating cells produces a population of cells."); Appx1781, ¶ 167 ("Phan is directed to 'a method for isolating stem/progenitor [cells … such as mesenchymal stem/progenitor cells]."); Appx1797–1798, ¶ 201("Kita is directed to 'a protocol to isolate adult [stem cells] from the cord lining membrane … and characterize the isolated cells ….'").

In support of its argument that "isolated cell" must refer to a single cell, Restem criticized Jadi Cell's expert for asserting that "express/does not express" and "isolated cell" must be understood by their contextual use. On cross-examination, however, Restem's expert

admitted the same thing. *See, e.g.*, Appx3984–3985 at 30:21–31:12. ("[D]o you mean that a certain percentage are positive and a certain percentage are negative? A. There's -- I'm -- so it would very much depend on the situation you're talking about, the markers you're talking about, the controls you're using, how and why you're setting measurements where you're setting them. It's -- it's a very situation-dependent thing."); Appx3986 at 32:5–17 ("Positive and negative is something that's subjective."); Appx3990–3991 at 36:17–37:16 ("As I said before, expressed or not expressed is very much in the eye of the beholder….").

Fact witnesses likewise referenced a population of cells when testifying about whether a marker is expressed/not expressed. *See, e.g.*, Appx 2887 at 24:18–25 (referencing "population that was over 90 percent expressed in CD90 and CD105 and less than 10 percent expressing CD30 or CD45."). *See also* Appx2891 at 40:11–16.

The prior art also refers to a percentage of expression of markers **within cell populations** in order to characterize marker expression as negative or positive. *See, e.g.,* Appx1936, Table 2; Appx1923, FIG. 2B.

Additionally, the ISCT criteria, asserted by Restem as prior art, specify that a population of MSCs must contain at least 95% cells that test positive for three markers, CD105, CD73, and CD90, and no more than 2% cells that test positive for CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR. Appx3803, ¶ 8.

Considering the intrinsic and extrinsic evidence together, and largely adopting Restem's proposed construction, the Board correctly concluded: "expresses" means "the marker is confirmed present relative to a control sample" and "does not express" means "the marker is confirmed absent relative to a control sample." Appx28. As part of its construction of those terms, and relying on substantial record evidence, the Board properly noted that "isolated cell" refers to "a cell population." *Id*.

2. Substantial Evidence Supports the Board's Finding that Restem Did Not Prove the Claimed Cells were Anticipated by Majore.

Majore fails to disclose all the elements of the recited product claims. Appx38 ("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]."). Restem does not dispute this fact. To remedy that deficiency, Restem alleged that the process employed by Majore is the same as the process recited in the '176 Patent and therefore must yield the Claimed Cells. *Id*. The Board noted that while Majore met the process step limitations of the product-by-process claims, Restem failed to demonstrate that Majore would "necessarily" result in cells having the exact same marker expression profile as the Claimed Cells. Appx40. More importantly, Majore itself contains no proof that it produced Claimed Cells as it offers no data on the expression of NANOG and fails to disclose the expression of the required surface markers. Appx34–38.

The Board "recognize[d] that the process steps of claim 1 are quite broad when construed in light of the patent." Appx42. Bearing the breadth of the process steps in mind, the Board found that the specification "does not address whether every disclosed embodiment or the broad process parameters disclosed therein would necessarily result in an isolated cell with a marker profile consistent with claim 1." Appx39–40. (citing numerous different aspects of the invention

disclosed in specification and differences in marker expression of those aspects). The Board also noted claim language specifying that the claimed cell population which expresses "at least three" of nine recited markers, and "at least five" of eleven recited markers implicitly "recognizes that cells prepared according to the process limitations…**would not all have the exact same marker profile**." Appx40. (emphasis added).

The record prior art and expert testimony likewise establish that the marker expression of the Claimed Cells is affected by more than the broadly construed process steps recited in claim 1. For example, the Board specifically noted Rojewski's recitation of numerous factors that affect differences in surface marker expression, including source tissue, age and sex of the donors, the method of isolation, cellular senescence, detection methods, and the like. Appx40–41. (noting the admission from Restem's expert that "specific growth media and culture conditions are more important for preferentially culturing cells with a particular marker pattern compared to what additional tissues are present in the culture.")

The record also demonstrated that intercellular communication is another factor that affects surface marker expression. Jadi Cell's expert explained:

> 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.

Appx3813, ¶ 30.

> These cell-cell interactions cause cells to alter expression of genes, thereby changing phenotype. A mixture of a large number of cell types, as would be produced by isolating cells from multiple types of tissue, has the potential for more varied and complex cell-cell interactions than a less heterogeneous mixture of cells derived from a single tissue.

Appx3816, ¶ 32.

Restem's expert agreed with the principle of intercellular communication, referring to it as cell-to-cell interaction. Appx4010–4012 at 56:18–58. He also admitted that expression of genes can change, and turn on or off, in response to tissue culture conditions. Appx1713–1714, ¶ 49. He further admitted that "there are many

known and unknown tissue culture conditions that could change expression of genes. I don't know them all." Appx3996 at 42:15–17.

The Board was also persuaded by Jadi Cell's presentation of testing evidence "introduced to show that the Claimed Cells have a different gene expression profile and cellular function as compared to the control cells isolated via conventional techniques." Appx42–43. Weighing that evidence, the Board remarked that while Restem's expert purportedly routinely used the Majore protocol, he failed to provide "testing evidence to confirm that cells by [Majore] necessarily met the non-expression criteria of [the Claimed Cells]." Appx38.

A particular deficiency in the prior art related to the claimed negative expression (or non-expression) of NANOG in the Claimed Cells. Substantial evidence demonstrates that positive NANOG expression is not only a desired characteristic of stem cells but a defining characteristic. *See* Appx3809, ¶¶ 20–21; *see also,* Appx1923. (NANOG is "key molecule[] necessary for the maintenance of self-renewal of SCs."). Restem's expert admits NANOG is a stem cell marker (Appx3995 at 41:7–10) and both his and Restem's own patents

all state that positive NANOG expression is a characteristic of UC derived stem cells. Appx3810–3811, ¶¶24–25.

Importantly, not a single prior art reference indicates negative NANOG expression is desired in stems cell or even an expected result. *See*, Appx4026 at 72:10–13 (where Restem's expert concedes he is not aware of a single reference where negative NANOG expression in stem cells is desirable). Indeed, while Majore is silent as to NANOG expression, all of the remaining prior art references that tested NANOG reported positive NANOG expression in cultured cells. *See* Appx3680, ¶ 149; *see also*, *supra* pp. 16-25.

In sum, the Board properly found that Restem had not proven that Majore inherently anticipated the Claimed Cells. Appx44. These findings were based on the breadth of the recited process steps, the lack of proof that following those broadly construed process steps would necessarily result in the specific surface marker profile of the Claimed Cells, and test data from the prosecution history. *Id*.

3. Substantial Evidence Supported the Board's Finding that Restem Did Not Prove Claim 9 was Obvious.

The Board concluded that that none of the prior art references, alone or in combination, rendered the challenged claims obvious. Appx75–76. On appeal, Restem does not challenge the Board's factual findings regarding obviousness of claim 1, nor does it challenge the Board's conclusion that claim 9 is non-obvious because claim 1 is non-obvious. Rather, it faults the Board solely with respect to the Board's additional rationale for finding claim 9 non-obvious. Appellant's Br. 59–60.

For context, Jadi Cell provides relevant background related to the Board's conclusion of non-obviousness with respect to claim 1 from which claim 9 depends. For example, despite Majore's failure to disclose all of the limitations of the Claimed Cells, Restem argued that the POSITA would be able to predict the specific combination of the recited gene markers. Appx52. Restem's support for this assertion comprised of testimony from its expert witness. *Id*. After weighing the evidence, the Board found Restem's expert testimony "[was] entitled to

little weight." *Id*. (noting that Restem's expert "does not cite anything to support his opinion…nor does [he] explain why the artisan would have had this understanding aside from simply stating it."); *see also*, Appx63 (noting Restem's expert testimony regarding Phan also accorded "little weight."). Consistent with the admonition in its Decision to Institute, the Board found that Pierantozzi, Rojewski, Meiron, and Riekstina fail to cure the deficiencies in Majore. Appx53.

The Board also found that the proposed combinations of Pierantozzi, Rojewski, Meiron, and Riekstina with Phan or Kita did not obviate the Claimed Cells. Appx71–72. Among other things, the Board noted the prior art's positive NANOG expression which is inapposite to the requirements of claim 1. *See, e.g.*, Appx70 (noting Kita's cells "strongly express NANOG").

In addition, Majore, which analyzes whole UC tissue, teaches away from using cells derived from bone marrow noting "BM aspiration is an invasive procedure and the portion of MSC in the BM mononuclear cell fraction is very small." Appx1932. Rojewski, Riekstina, Meiron, or Pierantozzi all contain bone marrow cells.

Appx3707–3710, ¶¶223–228. Likewise, Kita notes "several disadvantages" of using "adult SCs," and further cautions against using bone marrow and adipose as a "source for mesenchymal stem cells," due, for example, to "a high risk of viral and bacterial infection" and the need of "invasive procedures," respectively. Appx1919. Thus, instead of bone marrow and adipose for sources, Kita proposed using "[u]mbilical cord and amniotic membrane." Appx1920.

The Board also remarked on the unpredictability of the prior art. Appx53. As one example, the Board noted that "MSCs isolated from newly-cultured cells obtain from non-umbilical cord tissue an 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." Appx53–54. The Board also referenced statements of unpredictability in Rojewski. *Id*. (noting numerous factors affecting surface marker expression).

Testimony from both Restem's and Jadi Cell's experts confirmed the unpredictable state of the art. Jadi Cell's expert testified that "[s]mall, seemingly insignificant details, like a change to a minor

process reagent or culture vessel, can have unexpected and unwelcome effects on the manufacturing process and function of the cell therapy product." Appx3708, ¶ 226; *see also,* Appx3709, ¶ 226 (noting "cell isolation methods, the concentrations at which cells are grown, frequency and volume of culture medium changes, types of culture vessels" as factors effecting processes).

Restem's expert testified that marker expression is "exquisitely sensitive" to detection. Appx1787, ¶175. And explained that marker expression "depend[ed] on what marker you're looking at, what the nature of that marker is, and then all sorts of other unpredictable, environmental, technical challenges." Appx3979 at 25:10–13. He further noted that "[t]here are many known and many unknown tissue culture conditions that could change expression of genes. I don't know them all." Appx3996 at 42:15–17. In Restem's expert's words, "[s]cience is hard." Appx3979 at 25:13–14.

Given the lack of interchangeability between the prior art teachings, the overall unpredictability in the art, and the "little weight" according to Restem's expert, the Board found that Restem "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." Appx64, 71.

SUMMARY OF ARGUMENT

A. THE BOARD APPLIED THE CORRECT LEGAL STANDARD TO CLAIM CONSTRUCTION.

The Board determined that it only needed to interpret two claim terms to render its judgment; (1) "placing a SEL…in direct contact with a growth substrate" and (2) "expresses/does not express." *See* Appx17. Restem does not contest the Board's construction of either of these phrases. Rather, Restem asserts that the Board implicitly construed "isolated cell" as part of "express/does not express" and that this implicit construction constitutes legal error. Appellants' Br. 21.

Specifically, Restem argues that the '176 Patent defines "an isolated cell" to mean a single cell. In contrast, Jadi Cell argues that the term "isolated cell" means a cell population and that the term must

be read in the context of other claim terms, including express/does not express." The Board found that extrinsic evidence was required to properly construe "express/does not express." Appx26. The Board reviewed expert testimony and the teachings of the prior art. Appx26–27; *see also,* Appx3821–3823, ¶¶ 44–49. Considering the intrinsic and extrinsic evidence together, the Board correctly concluded that 'isolated cell' means "a cell population." The Board's factual findings related to its construction are supported by uncontested substantial evidence.

To the extent the Court believes the Board's construction was legal error, it is harmless. The Board did not rely on construction of this term in rendering its FWD.

B. THE BOARD'S INHERENCY DECISION IS SUPPORTED BY SUBSTANTIAL EVIDENCE AND APPLIED THE CORRECT LEGAL STANDARD.

Restem argues that because the Board found the broadly construed process steps were disclosed in the prior art, the Board must automatically find that the Claimed Cells are the natural result of those steps—irrespective of how broad the process steps may be or how narrow the product claims may be. Appellant's Br. 22-23. In support of

its argument, Restem misconstrues an exception to the law regarding product-by-process claims. That law allows a court to consider process steps in the patentability analysis to the extent those steps provide a structure or function to the underlying product that is not found in the prior art. *See, e.g., Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012)). *Greenliant Sys.* does not stand for the proposition that all recited process steps, no matter how broadly they are construed, will inherently anticipate the product in the product-by-process claim. That proposition finds no support in the law.

C. THE BOARD DID NOT READ ADDITIONAL "STEPS," "FACTORS," OR "CONDITIONS" INTO THE CLAIMS.

Restem argues that the Board implicitly construed the process steps of the challenged claims to include additional "steps," "factors", or "conditions." Appellant's Br. 21. Restem's argument lacks merit. In explaining why the broadly recited process steps would not necessarily result in the Claimed Cells, the Board noted many different process steps in the prior art, culture conditions, or factors that contributed to differences in gene marker expression. Appx41–43. The Board's

explanation of those differences are not claim limitations. Rather, they are uncontested facts that contribute to the unpredictability of gene marker expression…facts the Board indicated persuasively explained why the process steps of the challenged claims would not necessarily produce the Claimed Cells. *Id*.

D. THE BOARD'S CONCLUSION THAT DEPENDENT CLAIM 9 IS NON OBVIOUS IS PROPER.

Claim 9 depends on independent claim 1. Restem does not argue that the Board erred in finding claim 1 non-obvious. Rather, it contends that the Board did not support its conclusion that claim 9 was non-obvious with substantial evidence. Restem's argument lacks merit. "Dependent claims are non-obvious under § 103 if the independent claims from which they depend are determined to be non-obvious." *In re Kiely*, 2022 U.S. App. LEXIS 15693 (Fed. Cir. 2022) (nonprecedential) (citing *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988)). As such, the Board was not required to provide any additional rationale regarding unpatentability of claim 9. Irrespective, the Board provided ample factual support to explain its reasoning.

ARGUMENT

A. STANDARD OF REVIEW

This Court "review[s] the Board's legal conclusions de novo and its factual findings for substantial evidence." *Kamstrup*, 43 F.4th at 1380 (citing *ACCO Brands Corp. v. Fellowes, Inc.*, 813 F.3d 1361, 1365 (Fed. Cir. 2016)). Substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *In re Gartside*, 203 F.3d 1305, 1312 (Fed. Cir. 2000) (quoting *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938)).

An appellate court "do[es] not and should not reweigh evidence or make factual findings." *Impax Lab'ys Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1382 (Fed. Cir. 2018) (citing *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 327 (2015)). The Court's "role is to review the Board's findings for substantial evidence, not to step into its place and make those findings anew." *Roku, Inc. v. Universal Elecs., Inc.*, 63 F.4th 1319, 1326 (Fed. Cir. 2023) (citing *Impax Lab'ys*, 893 F.3d at 1382) (noting "although this court could well have decided the factual

dispute at hand differently than the Board did, it is not the province of this court to do so."); *see also Teva Pharms.*, 574 U.S. at 327 (where a lower tribunal, which "has presided over, and listened to, the entirety of a proceeding has a comparatively greater opportunity to gain that familiarity than an appeals court judge who must read a written transcript or perhaps just those portions to which the parties have referred").

B. THE BOARD PROPERLY CONSTRUED THE TERM ISOLATED CELL.

"Claim construction is ultimately a question of law that may be based on underlying factual findings." *Kamstrup*, 43 F.4th at 1381 (citing *Teva Pharms.*, 574 U.S. at 332–33). Thus, this Court "review[s] the Board's claim constructions de novo and review[s] any underlying factual determinations for substantial evidence." *Id.* (citing *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1278 (Fed. Cir. 2017).

The Board determined that it only needed to interpret two claim terms to render its judgment; (1) "placing a SEL…in direct contact with

a growth substrate"[4] and (2) "expresses/does not express." *See* Appx17 (citing *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. "isolated cell."

Restem does not contest the Board's construction of "placing a SEL … in direct contact with a growth substrate." or "express" or "does not express." Nor does it assert that the Board cited to an incorrect legal standard. Rather, Restem asserts that the Board implicitly construed "isolated cell" as part of "express/does not express" and that this implicit construction constitutes legal error.[5]

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[4] Jadi Cell adopts the Board's claim construction for purposes of this appeal.

[5] Restem also asserts that Jadi Cell changed its claim construction related to "express/does not express" and "isolated cell" mid-trial. Appellant's Br. 48. Restem misconstrues the record. In its Preliminary Response, Jadi Cell noted that "[a] POSITA would understand that the term 'isolated cell' must be read in context of 'culturing' and 'self-renewal and culture expansion' and know that the term includes

As part of claim construction, the Board found that the intrinsic evidence did not permit it "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." Appx26.[6] Looking to the extrinsic record, the Board reviewed "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." *Id.* The Board found that both Restem and Jadi Cell's "experts agree that, at the time of the invention, marker analysis was performed at a cell population

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multiple cells…**Accordingly, the terms 'expresses' and 'do not express' must be construed to include a percentage of cells in a population that express a marker.**" Appx315. (emphasis added). Jadi Cell never deviated from that proposed construction.

[6] *Cf.* Appx953 (where Examiner referenced Claimed Cells as population of cells throughout examination); Appx94 (where specification discusses "various cells, stem cells, and stem cell components, including associated methods of generating and using such cells" (1:31–33) and "cultures of isolated cells" (1:49–50).); and Appx100 at 14:1–3 (providing examples of cell populations ranging from 500,000 to 1,000,000 and more).

level." Appx26–27; *see also,* Appx3821–3823, ¶¶ 44–49. (explaining POSITA understanding of "an isolated cell" as a "literary device" and that "[b]ecause the details of the cell type may involve a long list of descriptive modifiers, for simplicity the text can be written in terms of one cell, even though it is understood that the author is referring to a product that can contain many millions or billions of these cells.").[7]

The Board also considered the asserted prior art "for purposes of determining how the term 'express' was used in the art." Appx28.

Considering the intrinsic and extrinsic evidence together, the Board correctly concluded:

a. 'isolated cell' means "a cell population;"

b. 'expresses' means "the marker is confirmed present relative to a control sample;" and

c. 'does not express' means "the marker is confirmed absent to a relative control sample."

Id.

[7] The Examiner also clearly understood the Claimed Cells referred to a population of cells. *See supra,* p. 32.

2. Restem Cannot Demonstrate Prejudicial Harm

The Board's factual findings with respect to claim construction are supported by substantial evidence and its ultimate construction is consistent with the prevailing law. To the extent the Court disagrees, however, any error by the Board is harmless. This Court's review under the APA is subject to a harmless-error rule. *See, e.g.*, 5 U.S.C. § 706 ("[D]ue account shall be taken of the rule of prejudicial error."). The party challenging the Board's decision must demonstrate the harmfulness of the alleged error. *See Shinseki v. Sanders*, 556 U.S. 396, 406, 409–10 (2009); *accord Vicor Corp. v. SynQor, Inc.*, 869 F.3d 1309, 1325 (Fed. Cir. 2017). Restem has failed to do so.

In order to demonstrate that implicit construction of "isolated cell" constituted prejudicial error, Restem must show that the Board relied on the construction to reach its final conclusion. *See Bot M8 LLC v. Sony Interactive Ent., LLC*, 66 F.4th 1380, 1385 (Fed. Cir. 2023). Restem cannot do so because the Board did not, nor did it need to, rely on any construction of that term to rule in Jadi Cell's favor. As noted herein (*see supra,* p. 41), not a single prior art reference disclosed a

single cell with the claimed gene marker expression profile. Restem cites no evidence of any process where the claimed gene marker expression profile was a necessary, or obvious result.

C. RESTEM'S INHERENCY ARGUMENT IGNORES THE FACTS AND THE LAW.

Anticipation, including inherent anticipation, is a question of fact, reviewed for substantial evidence. *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1341 (Fed. Cir. 2016) (citing *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015); *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014) (citing *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995)). A final written decision finding that a petitioner failed to carry its burden of proving invalidity will be affirmed so long as there are "sufficient factual findings to support its judgment." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

Restem argues that Majore inherently discloses the Claimed Cells because Majore's cells were produced using a process that reads on the process steps of the Claimed Cells. *See* Appx38. This argument ignores

the factual record and the law on inherency. As a beginning point, Restem admits that "[i]n evaluating patentability of a product-by-process claim, **the focus generally is on the product**." Appellant's Br. 51 (citing *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009) (other citations omitted)). However, the factual record makes clear that Majore and the other prior art of record contain no evidence that any Claimed Cells were produced or disclosed.

The Board noted the "claim language itself recognizes that cells prepared according to the process limitations [A] and [B] would not all have the exact same marker expression profile." Appx40. As a consequence, the Board found that "although Majore's disclosed process may satisfy the process limitations [] that does not establish that cells produced using Majore's process would necessarily have the same marker profile required by the claim." Appx40.

Restem's only evidence supporting the notion that Majore produced the Claimed Cells is Restem's expert testimony, which the Board afforded little weight. Appx52. Other than expert testimony, Restem provides no evidence that the ordinarily skilled artisan would

have even known that Claimed Cells could be cultured from the subepithelial layer of UC tissue. *See* Appx52. Indeed, Restem's expert did not "explain why the artisan would have had this understanding aside from simply stating it." *Id*. Additionally, the Board found that although the expert "testified that his laboratory routinely uses the Majore protocol, … he did not provide testing evidence to confirm that cells made by [the Majore] method necessarily [result in the Claimed Cells]." Appx38.

The Board also found that the prior art, including Majore, does not even teach that MSCs could be cultured from subepithelial UC tissue. *See* Appx52. Indeed, the Board found that "Majore uses the word 'subepithelial' only once to explain that primitive stem cells are 'distributed in subepithelial and intervascular regions….'" Appx52.

These facts findings, which cannot be altered on appeal, preclude 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) (citing *Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991)). For these reasons, the Board was "not persuaded that an ordinarily skilled artisan practicing the method of Majore would, inevitably, as inherency requires, produce the claimed isolated cell." Appx42. The Board further found that "[a]lthough the isolated cell of Majore *may* have the claimed expression profile, this is insufficient for a finding of inherency." Appx43 (emphasis in original).

Restem attempts to sidestep these factual conclusions by seeking support in easily distinguishable cases. For example, Restem cites *Arbutus Biopharma Corp.* for the proposition that "a limitation is inherent if it is the natural result flowing from the prior art's explicit disclosure." Appellant's Br. 50. (citing *Arbutus Biopharma Corp. v. Modernaxt, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023)). While that general proposition may be true, a more complete reading of *Arbutus* is instructive. First, *Arbutus* did not involve a product-by-process claim; the claim at issue was a composition claim. *Arbutus*, 65 F.4th at 660. That difference aside, the *Arbutus* court explained that inherent anticipation requires "that the disclosure of the prior art [be] sufficient

to show that the natural result flowing from the operation as taught in the prior art **would result in the claimed product**." *Id.* at 662 (quoting *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005)) (emphasis added).

With that standard in mind, the *Arbutus* court found no error in the Board's conclusion that the prior art inherently anticipated a claim limitation because "the prior art teaches the same formulations and the same DDM [Direct Dilution Method] as the [claimed product]." *Id.* at 664. Even according to *Arbutus*, it is not enough for Restem to show only that an operation exists in the prior art. Rather, Restem has the burden of showing that the **claimed product** is the natural result of that operation. *See id.* at 662. The Board properly found that Restem failed to carry that burden of proof. Appx42.

Beyond *Arbutus*, Restem cites several other cases for the proposition that process steps can be considered when evaluating patentability. Appellant's Br. 51-52. For example, Restem relies on *Greenliant Sys.* and its progeny. *Greenliant Sys.* and its progeny stand for the proposition that the process components of a product-by-process

claim can be "'**relevant as evidence of no anticipation**' although they 'are not explicitly part of the claim.'" *Kamstrup* at 1381 (quoting *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012)) (emphasis added). This is true only when the steps "impart[] 'structural and functional differences' distinguishing the claimed product from the prior art." *Id.* (quoting *Greenliant Sys.*, 692 F.3d at 1268). Here, Restem does not argue that the claimed process steps impart any structure or functional differences distinguishing the claimed product from the prior art.[8] To the contrary, Restem only argues that Claimed Cells must have been created by Majore, even though no facts support this contention. As such, Restem cannot twist *Greenliant Sys.* and its progeny to its benefit.

Restem also cites *Atlas Powder Co v. Ireco, Inc.*, 190 F.3d 1342, 1349 (Fed. Cir. 1999) for the proposition that an "[i]nsufficient prior

[8] Curiously, Restem faults the Board for not specifically analyzing whether the broadly construed process steps impart functional characteristics to the claims. The Board did not do so because, as the Board noted, "[w]here the challenged claim is a product-by-process claim, analysis of patentability focuses on the product." Appx11.

understanding of the inherent properties of a known composition does not defeat a finding of anticipation." Appellant's Br. 51. Record evidence establishes that, contrary to the Claimed Cells, positive NANOG expression is an expected result in cultured MSCs. Indeed, it is a "key molecule" in stem cells. Appx1923. **Every prior art reference that evaluated NANOG reported positive NANOG expression in cultured MSCs**.[9]

Based on this, the Board found that Restem "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 Power*, such as by showing test results of existing MSCs that does not express NANOG." Appx37. The Board, therefore, found "that the cell marker expression/non-expression pattern distinguishes the claimed isolated cell, and is therefore limiting." *Id*. In sum, the Board

[9] For example, of Restem's three primary references (Majore, Phan, and Kita), Majore did not report any results related to NANOG expression, and Kita and Phan (the other two prior art references that contained umbilical cord tissue) both reported positive NANOG expression. Appx1923, 2192.

correctly weighed substantial evidence in finding that Restem failed to carry its burden of proof—the substantial evidence standard requires nothing more for affirmance. *See, e.g., Skky, Inc. v. MindGeek s.a.r.l.*, 859 F.3d 1014, 1022 (Fed. Cir. 2017).

D. Restem's Inherency Argument Also Conflates the Purpose of the Patent Specification with the Purpose of the Patent Claims.

At its core, Restem's inherency argument is premised on a misunderstanding of the law and incorrect characterization of the record. As a beginning point, in various locations in its papers, Restem asserts that the parties were in "agreement" that "the claimed process steps impart the recited markers." *See, e.g.*, Appellant's Br. 55. And that in the face of that "agreement" the Board still found the prior art process steps that read on those process steps, did not result in the claimed markers. *Id*. at 56. Neither the Board nor Jadi Cell "agreed" that the claimed process steps, construed broadly, would produce the Claimed Cells.

The specification of the '176 Patent teaches, in one embodiment, that the Claimed Cells can be derived from opening the UC, removing

the WJ and blood vessels, and exposing the SL. That SL is then intentionally placed on the culture media. No other tissue from the UC is mixed in with the culture. Appx5. While there are, of course, many other steps taught in the specification and within the grasp of the POSITA, Jadi Cell argued at trial that these steps should be read into the recited process steps of the Claimed Cells. Appx480-482.

Specifically, Jadi Cell proposed that the process step of "placing a subepithelial layer…in direct contact with a growth substrate," should be construed as requiring the removal of Wharton's Jelly ("WJ") and blood vessels from the SL and placing the exposed SL face down directly in contact with a growth substrate. Appx18–19. Those specific process steps contributed to the isolation of a population of cells with the claimed gene marker expression. *See generally*, Appx492, 506. The Board did not adopt Jadi Cell's proposed construction, choosing not to import those limitations from the specification into the claims. Appx24. At no time did Jadi Cell "agree" that following only the recited process steps, as construed by Restem, would yield a population of self-renewing cells with the recited marker expression.

Restem's mischaracterization of Jadi Cell's and the Board's "agreements" aside[10], Restem's argument on inherency underscores its fundamental legal error. In its barest form, Restem argues that in a product-by-process claim, the process steps teach the POSITA how to make the claimed product. That is, if the POSITA were to simply follow the claimed process steps, they would invariably get the claimed product.[11] Restem's argument conflates the function of patent claims with the function of the patent specification. It is axiomatic that the patent claims define the scope of the invention, and the patent specification teaches the POSITA how to make or use the invention without undue experimentation, not the other way around. *See, e.g.*, *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir.

[10] Restem mischaracterizes what the Board and Jadi Cell "agreed" to in many parts of its brief. Only those that Jadi Cell thought helpful to the Court are addressed herein.

[11] Ironically, following Restem's logic would necessarily result in an importation of limitations from the specification into the claims. Restem vehemently opposed importing any limitations into the process steps at trial. Appx570. The Board sided with Restem on that point. Appx24.

1997) (describing the purpose of the patent specification); 35 U.S.C. § 112 (setting forth the standard for patent specifications).

Put plainly, the claims of the '176 Patent do not teach the POSITA how to make and use the invention but define the "metes and bounds" of the invention. *Markman v. Westview Instruments, Inc.,* 52 F.3d 967, 1000 (Fed. Cir. 1995), *aff'd,* 517 U.S. 370, 134 L. Ed. 2d 577, 116 S. Ct. 1384 (1996). The specification is different. It teaches the POSITA how to make and use the Claimed Cells. And nowhere in the prior art is there any teaching or disclosure of process steps that would necessarily yield the Claimed Cells.

E. THE BOARD'S CONCLUSION THAT THE CLAIMS OF THE '176 PATENT WERE NOT ANTICIPATED BY THE PROCESS STEPS IS SUPPORTED BY SUBSTANTIAL EVIDENCE.

The Board's factual findings that the recited process steps will not necessarily yield the Claimed Cells are supported by substantial evidence. Looking first to the patent itself, the Board noted that the specification "does not address whether every disclosed embodiment or the broad process parameters disclosed therein would necessarily result in an isolated cell with a marker profile consistent with claim 1."

Appx39–40. The Board also noted that claim language reciting "at least three" of nine markers, and "at least five" of eleven markers "recognizes that cells prepared according to the process limitations…would not all have the exact same marker profile." Appx40.

The prior art and expert testimony also establish that the marker expression of the Claimed Cells is not solely dependent on the broadly construed process steps recited in claim 1. For example, the Board noted Rojewski's express recitation of numerous factors that affect surface marker expression. Appx40–41. Jadi Cell's expert testified that marker expression is affected by cellular senescence, cell-to-cell interaction, or other biochemical signals. *See*, e.g., Appx28 n.18. Restem's expert agreed with the principle of cell-to-cell interaction and admitted that expression of genes changes in response to tissue culture conditions. *Id*.

The Board also remarked that even though Restem's expert "routinely uses the Majore protocol…he did not provide test evidence to confirm that the cells made by this method necessarily met the non-expression criteria" of the Claimed Cells. Appx38. At oral argument,

counsel for Restem responded simply that this evidence just "wasn't necessary." *Id*. And while the comparison between the Claimed Cells and Jadi Cell's evidence was not perfect, the Board noted that Jadi Cell had provided at least some testing evidence that "use of a different process to create an isolated cell can result in a different marker expression profile." Appx43.

Remarkably, Restem argues that it was Jadi Cell's burden to demonstrate that the process steps, broadly construed by the Board, do not inherently produce the Claimed Cells. Appellant's Br. 53 n.7. Restem cites *3M Innovative Props. Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1371 (Fed. Cir. 2003) in support of this proposition. Restem's argument lacks merit. The burden of proof in an inter partes review resides with the Petitioner. Appx10. The *3M* court did not shift that burden of proof to the patent owner. Specifically, the *3M* court found that the patentee's specific definition of terms in its specification "neither transforms [the claim at-issue] into a product-by-process claim nor even limits the scope of the claim to a serial method of manufacture." *3M*, 350 F.3d at 1371. *3M* further notes "[a] novel

product that meets the criteria of patentability is not limited to the process by which it was made." *Id.* (quoting *Vanguard Prods. Corp. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372 (Fed. Cir. 2000)). *3M* is inapplicable here. To be clear, the holding in *3M* does not stand for the proposition that the patentee must prove that process steps recited in a product-by-process claim do not teach the POSITA how to make the claimed product.

F. JADI CELL IS NOT BOUND BY CLAIM CONSTRUCTION ARGUMENTS THAT WERE NOT ADOPTED BY THE BOARD.

Restem argues that Jadi Cell is "bound" by trial argument regarding claim construction that was not ultimately adopted by the Board. Appellant's Br. 53 n.7. (citing *Greenliant Sys.*, 692 F.3d at 1271). Restem's argument lacks merit. To the extent Restem is referencing the doctrine of judicial estoppel, that doctrine can bind a party to a position that it both advocated and successfully achieved in a lower tribunal. *See generally SkyHawke Techs., LLC v. DECA Int'l Corp.*, 828 F.3d 1373 (Fed. Cir. 2016). In this case, Jadi Cell argued for a claim construction that was not adopted by the Board. As such,

judicial estoppel cannot apply. In any event, "[d]isclaimers in an IPR proceeding are not binding in the proceeding in which they are made." *CUPP Computing AS v. Trend Micro Inc.*, 53 F.4th 1376, 1384 (Fed. Cir. 2022).

Irrespective, Restem's cited case, *Greenliant Sys*, is distinguishable. *Greenliant Sys* concerns prosecution history disclaimer. *Greenliant Sys.*, 692 F.3d at 1271. In that case, the patentee, Xicor, "clearly and unmistakably represented to the Examiner and the Board that TEOS was a necessary component of the deposition process that imparted the distinct structural characteristics upon Xicor's claimed tunneling oxide layer." *Id.* The court found that Xicor "had surrendered devices produced through the use of non-TEOS reactants during the prosecution of the [patent at-issue]." *Id.* (citing *Kim v. ConAgra Foods, Inc.*, 465 F.3d 1312, 1323 (Fed. Cir. 2006)). When Xicor argued that something other than TEOS determined the physical characteristics of the claimed tunneling oxide layer, the Board found that Xicor was bound by its previous disclaimer. *Id.* *Greenliant Sys* does not apply here because the claim construction arguments Jadi

Cell made to the Board were not made during prosecution of the '176 Patent and were also not adopted by the Board.

G. THE BOARD DID NOT READ ADDITIONAL LIMITATIONS INTO THE CLAIMS.

Restem argues that the Board erred because it required Restem to prove the presence of limitations that were not recited in the challenged claims. More specifically, Restem argues that the Board read additional "placing steps," and unspecified "factors," and "conditions" into the process steps of the claims. Appellant's Br. 32. Restem also argues that "additional limitations" constituted a new ground of rejection[12] which defeats the notice function of patent claims. Restem's argument lacks merit for several reasons.

First, the Board did not implicitly read limitations into the claims. The Board found that while the broadly construed process steps were taught in the prior art, Restem had not demonstrated that those

[12] Restem also argues that the Board should be reversed because it did not adequately explain its reasoning. Appellant's Br. 26. The cases Restem cites, however, do not require reversal. Rather, all of those cases note that the remedy for insufficient findings of fact or reasoning is a remand…not a reversal.

broadly construed process steps necessarily, or even obviously, resulted in the Claimed Cells. Appx40. As support for that finding, the Board pointed to the many different factors affecting gene marker expression. Appx41–42. The Board also noted many differences in the various process steps described in the prior art as reasons why the broadly construed process steps would not necessarily yield a gene marker profile identical to the Claimed Cells. Appx39–40.[13]

As a consequence, and contrary to Restem's argument, the Board did not require Restem to show that the claimed "marker expression profile is only dependent on the process used to produce the cells." Appellant's Br. 56. Rather, the Board noted that if Restem had shown that the claimed marker expression profile in fact depended solely on the specific claimed process steps, then Restem's argument may have survived scrutiny. Appx40 n.22 ("Only if Petitioner had adduced

[13] At least one of these differences is found in the Board's claim construction, as it notes the process described in the '176 Patent requires one to "intentionally" place UC tissue comprising SL material so that it touches a growth substrate.

evidence that the marker expression profile solely depended on the process used to produce the Claimed Cells could Petitioner rely on cases cited by Petitioner's counsel at oral argument."). Restem did not, and indeed could not, make that showing.[14]

Second, the Board's factual finding that different factors and conditions can affect gene marker expression was not a new ground or rejection, nor was it even a surprise to Restem. Jadi Cell briefed the different factors affecting gene marker expression and provided extensive expert testimony regarding the same. Appx489–493. If Restem truly had been caught off guard, it could have sought permission to file a sur-reply or asked for a rehearing. Restem did neither.

Lastly, Restem argues that the Board's explanation regarding inherency violates the "notice policy" of patent law. Appellant's Br. 44. Restem's argument here also lacks merit. The notice policy of patents is

[14] Even if the Board imported limitations into the process steps, that importation would constitute harmless error. Here, the focus of the patentability analysis is on the patented product, not the process. *Amgen*, 580 F.3d at 1369.

intended to give notice to the public regarding the scope of a claimed invention. This permits the public fair notice of what it may and may not do. Assuming that Restem's argument is valid, and the Board imported limitations into the claims, the importation would prejudice Jadi Cell, not the public. "Unless it is shown that the process . . . was followed to produce the defendant's article, or unless it is shown that that article could not be produced by any other process, the defendant's article cannot be identified as the product of the process." *Abbott Labs v. Sandoz, Inc.*, 566 F.3d 1282, 1292 (2009) (quoting *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 310 (U.S. 1884). In other words, if the Board had indeed imported limitations into the process steps, Jadi Cell would be required to prove additional elements to demonstrate infringement.

H. THE BOARD PROPERLY FOUND CLAIM 9 OF THE '176 PATENT WAS NOT OBVIOUS.

While Restem includes a stray reference to obviousness in a few locations in its appeal brief, the only substantive obviousness issue it raises on appeal is directed to dependent claim 9. Appellant's Br. 59.

The Board determined that claim 9 was not obvious in view of Kita, combined with Pierantozzi, Rojewski, Meiron, or Majore "for the same reasons as claim 1," but also because "the evidence of record showing a component of bovine serum in the culture media favors Patent Owner." *Id*.

Restem does not argue on appeal that the Board erred, or that there was not substantial evidence to support the finding that independent claim 1 is obvious or that claim 9 is not obvious for the same reasons that claim 1 is not obvious. Rather, Restem only takes issue with the Board's additional reasoning in support of its finding of non-obviousness of claim 9. Namely, that "the evidence of record showing a component of bovine serum in the culture media favors Patent Owner." *Id*.

A claim is invalid for obviousness "if the differences between the subject matter sought to be patented 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." 35 U.S.C. § 103. The Board's legal

determinations of non-obviousness are reviewed de novo. *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1358-59 (Fed. Cir. 2020) (citing *In re Van Os*, 844 F.3d 1359, 1360 (Fed. Cir. 2017)). Obviousness is a question of law based on underlying factual findings. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966). "The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact," *In re Gartside*, 203 F.3d at 1316 (citing *In Re Dembiczak*, 175 F.3d 994, 1000 (Fed. Cir. 1999). Similarly, the presence or absence of a "reasonable expectation of success" from making a combination is a pure question of fact. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). The Board's factual findings are reviewed for substantial evidence. *Adidas AG*, 963 F.3d at 1358-59.

Restem's bovine serum argument lacks merit, if for no other reason than its misunderstanding of the law and relationship between independent and dependent claims. "Dependent claims are non-obvious under § 103 if the independent claims from which they depend are determined to be non-obvious." *In re Kiely*, 2022 U.S. App. LEXIS 15693 (Fed. Cir. 2022) (nonprecedential) (citing *In re Fine*, 837 F.2d

1071, 1076 (Fed. Cir. 1988)). As stated by the Board, and undisputed by Restem, dependent claim 9 is non-obvious because claim 1 is non-obvious. The Board was not required to support its non-obviousness finding with respect to claim 9, because it fully supported its non-obviousness finding with respect to claim 1. Because it was not required to provide a separate basis for its finding with respect to claim 9, any error in its "additional" findings is harmless.

Restem's misunderstanding of the law aside, the Court does not require perfect explanations and will uphold the Board's decision so long as it can "reasonably discern that it followed a proper path, even if that path is less than perfectly clear." *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015) (citing *Bowman Transp., Inc. v. Arkansas-Best Freight Sys., Inc.*, 419 U.S. 281, 285–86 (1974)). Here, the Board supported its additional rationale sufficient for the Court to understand that it "followed the proper path." For example, the Board referenced its prior explanation regarding "the incompatibility of teachings from the references." Appx65. The Board also cited testimony from Jadi Cell's expert corroborating the Board's

rationale. *See, e.g.*, Appx3688–3689, ¶¶ 172–173 ("the '176 Patent specification and its examples [did not involve] serum of any kind…POSITA would know that Majore's use of growth medium 'supplemented with 10% human serum' contradicts the limitations of claim 9. Moreover, Majore mentions that 'the adherent cells were harvested by accutase . . . treatment,' which a POSITA would understand is a reagent that contains animal products.") (cleaned up).

In sum, the Board properly assessed the factual record and found that Restem had not carried its burden. These facts cannot be altered on appeal. The Board's judgment is consistent with the law of this Circuit and it cites to, and applies, the proper law regarding claim construction, anticipation, and obviousness. Accordingly, the Board's judgment should be affirmed.

CONCLUSION

Based on the foregoing, Jadi Cell respectfully requests that the Court affirm the Board's finding that Restem failed to carry its burden of proving that claims 1-15 of the '176 Patent are unpatentable

pursuant to 35 U.S.C § 102 or that claim 9 of the '176 Patent was unpatentable pursuant to 35 U.S.C § 103.

November 8, 2023

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CERTIFICATE OF SERVICE

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July 2020

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

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