United States Court of Appeals for the Federal Circuit

SKINMEDICA, INC.,
Plaintiff-Appellant,

v.

HISTOGEN INC., HISTOGEN AESTHETICS LLC, AND GAIL K. NAUGHTON,
Defendants-Appellees.

2012-1560

Appeal from the United States District Court for the Southern District of California in No. 09-CV-0122, Judge Janis L. Sammartino.

Decided: August 23, 2013

RICHARD P. BRESS, Latham & Watkins, LLP, of Washington, DC, argued for plaintiff-appellant. With him on the brief were GABRIEL K. BELL, of Washington, DC, and STEPHEN P. SWINTON, ALEXANDER E. LONG, and LISA LIMOR RABIE, of San Diego, California.

GREGORY A. CASTANIAS, Jones Day, of Washington, DC, argued for defendants-appellees. With him on the brief were ANDREW A. PINSON, of Washington, DC, and RANDALL E. KAY, of San Diego, California.

Before RADER, *Chief Judge,* CLEVENGER and PROST, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* PROST. Dissenting opinion filed by *Chief Judge* RADER.

PROST, *Circuit Judge.*

SkinMedica, Inc. ("SkinMedica") appeals from the decision of the United States District Court for the Southern District of California granting Histogen, Inc., Histogen Aesthetics, and Gail Naughton (collectively "Histogen") summary judgment of noninfringement of the asserted claims of U.S. Patent Nos. 6,372,494 ('494 patent) and 7,118,746 ('746 patent) after construing a phrase common to both patents. Because we find no legal error in the district court's construction, we affirm the grant of summary judgment.

I. BACKGROUND

SkinMedica owns the '494 and '746 patents. In 2009, it filed a patent infringement suit against Histogen for producing dermatological products according to methods covered by the claims of those patents.[1] Those claims generally relate to methods for producing pharmaceutical compositions containing "novel conditioned cell culture medium compositions, . . . [and] uses for the[m]." '494 patent col. 4 ll. 40–45.[2] A cell culture medium is an artificial environment, such as a liquid, that is outside the

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[1] The suit included allegations of trade secret misappropriate and violations of several state laws. Only the infringement claims are at issue on appeal.

[2] We cite only to the written description of the '494 patent because it is the parent of the '746 patent and uses an identical written description.

body ("in vitro") and "suppl[ies] the components necessary to meet the nutritional needs required to grow cells." *Id.* at col. 1 ll. 24–25. A "conditioned" cell culture medium is one which has been incubated with cells. *Id.* at col. 1 ll. 30–32 ("Once the culture medium is incubated with cells, it is known to those skilled in the art as . . . 'conditioned medium.'"). In addition to the nutritional compounds that are present in the unconditioned medium for feeding cells, a conditioned medium commonly includes "a variety of cellular metabolites and secreted proteins" produced by cells in the culture, including "biologically active growth factors, inflammatory mediators and other extracellular proteins." *Id.* at col. 1 ll. 34–37; *see also id.* at 8 l. 64–col. 9, l. 30. According to the patentees, those "extracellular" proteins may be useful in the treatment of many conditions, including "wrinkles, frown lines, scarring and . . . other skin conditions." *Id.* at col. 5 l. 50.

A. The Asserted Patents and Claims

Originally, the inventors of the '494 patent proposed claims related to a pharmaceutical composition comprising any cell culture medium conditioned by animal cells (or "eukaryotic" cells), including those cultured in either "two-dimensions" or "three-dimensions." Indeed, the written description explains that the invention "relates to compositions comprising cell culture medium conditioned by cells grown in two-dimensional culture (i.e., a monolayer), or in three-dimensional culture." *Id.* at col. 1 ll. 5–8. The written description also states the cells that condition the medium used in the invention "are cultured in monolayer, beads (i.e., two-dimensions) or, preferably, in three-dimensions" and "may be cultured in any manner known in the art including in monolayer, beads or in three-dimensions and by any means." *Id.* at col. 7 ll. 28–29; col. 9 ll. 66–col. 10 l. 1.

During prosecution of the '494 patent, the inventors limited their claimed inventions to pharmaceutical com-

positions comprising cell culture medium conditioned by animal cells cultured *only* in three-dimensions. They did so to overcome an anticipation rejection based on prior art (the "Shipley" reference) that disclosed the use in a pharmaceutical composition of cell culture medium conditioned by animal cells grown in two-dimensions.

In their final form, the claims of the '494 patent—and, correspondingly, the '796 patent—include the limitation that the cell culture medium used in the inventions must be conditioned by "culturing . . . cells in three-dimensions." Claim 1 of the '494 patent is representative.

> 1. A method of making a composition comprising:
>
> (a) *culturing* fibroblast *cells in three-dimensions* in a cell culture medium sufficient to meet the nutritional needs required to grow the cells in vitro until the cell culture medium contains a desired level of extracellular products so that a conditioned medium is formed;
>
> (b) removing the conditioned medium from the cultured cells; and
>
> (c) combining the conditioned medium with a pharmaceutically acceptable carrier to form the composition.

Id. at claim 1 (emphases added).

According to the patentees, a novel and important aspect of their invention is the difference between the conditioned medium produced by cells cultured in two-dimensions and in three-dimensions. "While growth of cells in two dimensions is a convenient method for preparing, observing and studying cells in culture," two-dimensional cultures lack "characteristic[s] of whole tissue in vivo." *Id.* at col. 2 ll. 15–18. In a section titled

"Background of the Invention," the inventors detail the relevance of that deficiency.

> Cell lines grown as a monolayer or on beads, as opposed to cells grown in three-dimensions, lack the cell-cell and cell-matrix interactions characteristic of whole tissue in vivo. Consequently, such cells secrete a variety of cellular metabolites although they do not necessarily secrete these metabolites and secreted proteins at levels that approach physiological levels. Conventional conditioned cell culture medium, medium cultured by cell-lines grown as a monolayer or on beads, is usually discarded or occasionally used in culture manipulations such as reducing cell densities.

Id. at col. 1 ll. 37–47.

The inventors explain in the written description that some researchers have attempted to create cell cultures that replicate the valuable characteristics of whole tissue in vivo. As they say, a "few investigators have explored the use of three-dimensional substrates" to grow cells with such characteristics. *Id.* at col. 2 ll. 19–20. In such systems, "three-dimensional substrates are inoculated with the cells to be cultured," and those cells "penetrate the matrix and establish a 'tissue-like' histology." *Id.* at col. 2 ll. 30–33. "Additionally," according to the inventors, "various attempts have been made to regenerate tissue-like architecture from dispersed monolayer cultures," which "could grow to more than ten cells deep" and could develop "organoid structures." *Id.* at col. 2 ll. 37–41. The inventors also detail how certain skin cell lines could form "friction ridges if kept for several weeks without transfer," and other cell lines could form "capillary tubules" in the presence of certain growth factors. *Id.* at col. 2 ll. 45–51. "However," the inventors state, "the long term culture and proliferation of cells in such systems has not been achieved." *Id.* at col. 2 ll. 55–57.

As part of the written description, the inventors discuss a system that is closer to achieving the goal of long term culture and proliferation of cells and that more closely replicates the valuable characteristics of whole tissue in vivo. They indicate that a three-dimensional cell culture system "will sustain active proliferation of . . . cells in culture for much longer time periods than will monolayer systems" and "supports the maturation, differentiation, and segregation of cells in culture in vitro to form components . . . analogous to counterparts found in vivo and . . . proteins [in] the condition[ed] medium more closely resembling physiological ratios." ' *Id.* at col. 11 ll. 11–19.

As the inventors describe them in the specification, three-dimensional cell cultures are created by inoculating a "three-dimensional framework" with cells. That framework is expressly defined as "a three-dimensional scaffold" that is "inoculated with stromal cells" and is "composed of any material and/or shape that (a) allows cells to attach to it . . . and (b) allows cells to grow in more than one layer." ' *Id.* at col. 6 ll. 42–47. The inventors explain that a number of non-exhaustive factors may contribute to the success of such a three-dimensional culture system, including, for example, that the "three-dimensional framework provides a greater surface area for protein attachment"; the three-dimensionality of the framework permits "stromal cells [to] continue to grow actively, in contrast to cells in monolayer cultures, which grow to confluence, exhibit contact inhibition, and cease to grow and divide"; "[t]he three-dimensional framework allows for a spatial distribution of cellular elements which is more analogous to that found in the counterpart tissue in vivo"; "[t]he elaboration of growth and regulatory factors by replicating stromal cells" in a three-dimensional culture may stimulate "proliferation" and the "regulat[ion] [of] differentiation of cells in culture"; "[t]he increase in potential volume for cell growth in the three-

dimensional system may allow the establishment of localized microenvironments conducive to cellular maturation"; and "[t]he three-dimensional framework maximizes cell-cell interactions by allowing greater potential for movement of migratory cells . . . in the adherent layer." *Id.* at patent col. 11 ll. 20–53.

In addition, the patentees highlight the importance of maintaining and maximizing "proliferative activity" during three-dimensional culturing and describe ways to do so. For example, they teach that "proliferating cells may be released from the matrix" used in a three-dimensional culture and "stick to the walls of the culture vessel where they may continue to proliferate and form a confluent monolayer." *Id.* at col. 14 ll. 20–24. That "should be prevented or minimized" by "[r]emoval of the confluent monolayer or transfer of the culture to fresh media in a new vessel" because the presence of confluent monolayers in the culturing vessel will "shut down" continued proliferation in a three-dimensional culture system. *Id.* at col. 14 ll. 24–31.

During prosecution of the '494 patent, the patentees also discussed the importance of sustained proliferation of cells in three-dimensional cultures and the importance of the components in the culture medium for achieving such growth. At one point, the examiner of the '494 patent rejected a set of proposed claims, which included the three-dimensional culturing limitation, over Shipley combined with U.S. Patent No. 5,032,508 ('508 patent) (issued to Naughton, et al.).[3] That patent discloses a "three-dimensional skin culture system" that uses a "three-dimensional matrix" to culture a variety of cells and that "allow[s] for normal cell-cell interactions and the

[3] Gail Naughton, a defendant in this case and an inventor of the '494 and '796 patents, was also an inventor of the '508 patent.

secretion of natural growth factors, and the establishment of a connective tissue network virtually identical to that found in vivo." '508 patent col. 27 ll. 10–35. The written description of the '508 patent additionally explained that "three-dimensional skin cultures have applicability to many fields of industry including use . . . as a source of naturally secreted pharmacologic agents." *Id.* at col. 27 l. 68–col. 28 l. 4. To overcome the obviousness rejection, the inventors of the '494 patent argued that "the conditioned medium from cells cultured in three-dimensions has *desirable properties not exhibited by medium conditioned by cells cultured [in] two dimensions*" and that "nowhere in Naughton et al., is there a teaching or suggestion that *sustained proliferation of the cells in culture* is a result of factors or components of the *conditioned medium*."[4] Response to Office Action, Exhibit to Response to Claim Construction Brief, *SkinMedica v. Histogen*, No. 3:09-cv-122, (S.D. Cal. July 21, 2009), ECF No. 47-1 at 30 (second emphasis added).

B. District Court Proceedings

In May 2011, the United States District Court for the Southern District of California construed the phrase "culturing . . . cells in three-dimensions" as "growing . . . cells in three dimensions (excluding growing in monolayers or on microcarrier beads)."[5] J.A. 49. The court reasoned that "the inventors acted as their own lexicographers, defining 'culturing . . . cells in three-dimensions' away from its ordinary meaning," by consistently distinguishing beads from three-dimensional cul-

[4] The prosecution of the '494 patent was prior to *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), a time during which the teaching, suggestion, and motivation test reigned supreme.

[5] The parties do not dispute the exclusion of monolayers.

tures in the specification. J.A. 21. That conclusion was evident from the written description, according to the court, because the inventors used the disjunctive "or" and the disjunctive phrase "as opposed to" as coordinating conjunctions when they listed monolayer, beads, and three-dimensions as the methods used in the invention to culture cells. *Id.* The court noted that there was only one other reference to culturing with beads in the specification: a statement by the inventors that the conditioned medium created from bead cultures was "conventional" and "usually discarded." *Id.* The court also concluded that the patentees "explicitly defined beads as a two-dimensional culture method" by using the phrase "beads (i.e. two-dimensions)." J.A. 22.

The district court stated, however, that it would have found otherwise if "the intrinsic evidence disclosed even a single reference to culturing cells in three dimensions using beads." J.A. 22. To that point, SkinMedica had argued that a document referenced in the written description provided such disclosure. That reference, *Cell & Tissue Culture: Laboratory Procedures* ("Doyle"), is a voluminous technical treatise that the written description states to be "incorporated by reference" in its "entirety," without further relevant citation to specific contents. '494 patent col. 7 ll. 50–53. Doyle states that microcarriers (beads) commonly formed "aggregates made up of as many as 10 or more microcarriers" that "are joined by cellular bridges." J.A. 100974. The court concluded that the relevant discussion in Doyle was not identified with enough particularity to be adequately incorporated into the intrinsic record.

The district court also gave no weight to the testimony provided by SkinMedica's expert, Dr. Salomon, during claim construction proceedings. Dr. Salomon had testified that beads should not be excluded from the meaning of "culturing . . . cells in three-dimensions." The court found

his testimony to be "inconsistent with the intrinsic patent record" and erroneously reliant on Doyle. J.A. 23.

Following claim construction, Histogen moved for summary judgment on the infringement claims. Based on its construction of the phrase "culturing . . . cells in three-dimensions," the district court granted Histogen's motion in November 2011. In its summary judgment opinion, the court first dismissed an argument by SkinMedica in opposition to the summary judgment motion that the phrase "excluding grown . . . on microcarrier beads" only excluded "two-dimensional growth *on* beads," not three-dimensional growth "*using*" beads. J.A. 53 (emphases added). The court clarified that its "use of the preposition 'on' as opposed to the preposition 'between' or the gerund 'using'" was "nothing more than the Court's dictional preference" and that its definition of "culturing cells in three-dimensions" would also exclude three-dimensional growth using beads. J.A. 52. After that explanation, the court determined there was no genuine dispute that Histogen's culturing method begins as "one- or two-dimensional growth" on beads that then "evolves into a three-dimensional growth phase in which the cells crawl off the beads." J.A. 54. The court held that summary judgment of noninfringement was appropriate because "Histogen's cell growth process, which uses beads, cannot infringe the disputed claim element as construed." J.A. 56.

SkinMedica filed a timely appeal of the district court's grant of summary judgment. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

II. DISCUSSION

SkinMedica raises a single point of error on appeal. It argues that the district court erroneously excluded beads from the definition of "culturing . . . cells in three-dimensions." According to SkinMedica, those of ordinary skill in the art would understand the ordinary meaning of

the phrase "culturing . . . cells in three-dimensions" to include the use of beads because they would have understood that beads could be used to grow cells in three dimensions. It believes that the inventors did not act as their own lexicographers because they did not expressly define culturing cells in three-dimensions nor disclaim the use of beads in such culturing. They argue that point is particularly clear given that: (1) the definition of three-dimensional framework provided by the inventors is broad enough to include beads; (2) Doyle is incorporated in the specification and discloses three-dimensional cell culturing with beads; (3) a published international patent application, WO 98/21312 ("Seldon"), which is listed among the "References Cited " on the cover page of the '746 patent, discloses that cells in bead cultures are "reminiscent" of those in vivo; and (4) Dr. Salomon testified that that beads could be used to grow cells in three dimensions and such cultures would exhibit the benefits of three-dimensional cultures described by the patentees.

We find no basis to disturb the district court's construction of the phrase "culturing . . . cells in three-dimensions." The specification clearly proves that the patentees defined the three-dimensional culturing required by the claims to exclude culturing with beads, because the patent expressly confines culturing with beads to two-dimensional culturing. Whether viewed as a matter of disclaimer or of lexicography, the result is the same: the kind of three-dimensional culturing protected by the patent excludes use of beads. Because the accused method employs beads, it cannot infringe the patents in suit. We therefore affirm the district court's grant of summary judgment of noninfringement to Histogen.

A. Legal Background

A grant of summary judgment is appropriate "if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a

matter of law." Fed. R. Civ. P. 56(a). The law of the regional circuit, here the Ninth Circuit, controls our review of a district court's grant or denial of a motion for summary judgment. *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, No. 2012-1397, 2013 WL 1606014 (Fed. Cir. Apr. 16, 2013); *Teva Pharm. Indus. v. AstraZeneca Pharm. LP*, 661 F.3d 1378, 1381 (Fed. Cir. 2011). The Ninth Circuit reviews grants of summary judgment rulings without deference. *Id.*; *see also Burke v. Cnty. of Alameda*, 586 F.3d 725, 730–31 (9th Cir. 2009).

The dispute in this case rests on the district court's construction of a single phrase in the asserted claims. Our review of that construction is de novo. *Cybor Corp. v. FAS Techs., Inc.,* 138 F.3d 1448, 1455–56 (Fed. Cir. 1998) (en banc).

"The words of a claim are generally given their ordinary and customary meaning as understood by a person of ordinary skill in the art when read in the context of the specification and prosecution history." *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1365–67 (Fed. Cir. 2012) (citing *Phillips v. AWH Corp.,* 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc)). When construing claim terms, we first look to, and primarily rely on, the intrinsic evidence, including the prosecution history and the specification—which is usually dispositive. *Phillips*, 415 F.3d at 1315 ("The claims, of course, do not stand alone. Rather, they are part of a fully integrated written instrument . . . . For that reason, claims must be read in view of the specification, of which they are a part. . . . Usually, it is dispositive . . . ." (citations omitted) (internal quotation marks omitted)). When interpreting the claims, the written description is of particular import, and it is "entirely appropriate for a court, when conducting claim construction, to rely heavily on [it] for guidance as to the meaning of the claims." *Phillips*, 415 F.3d at 1317; *see also id.* at 1316 ("The close kinship between the written description and the claims is enforced by the statutory

requirement that the specification describe the claimed invention in 'full, clear, concise, and exact terms.'" (quoting 35 U.S.C. § 112)).

When construing claim terms, "extrinsic evidence in the form of expert testimony can be useful to a court for a variety of purposes, such as to provide background on the technology at issue, to explain how an invention works, to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field." *Phillips*, 415 F.3d at 1318. However, "extrinsic evidence in general" is "less reliable than the patent and its prosecution history in determining how to read claim terms." *Id.* Expert testimony, in particular, is less reliable because it "is generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence." *Id.* For that reason, "conclusory, unsupported assertions by experts as to the definition of a claim term are not useful to a court." *Id.* Thus "a court should discount any expert testimony that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history." *Id.* (internal quotation marks omitted).

During claim construction, terms are not always afforded their ordinary meaning. In this case, the ordinary meaning of "culturing . . . cells in three-dimensions" would reach the use of beads. The question is whether the patentees here instead defined "culturing . . . cells in three-dimensions" to exclude the use of beads. If the specification reveals "a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess[,] . . . the inventor's lexicography governs." *Id.* at 1316; *see Helmsderfer v. Bobrick Washroom Equip., Inc.,* 527 F.3d 1379, 1381 (Fed. Cir. 2008) (explaining that inventors' definition of a claim term

controls when they "clearly express an intent" to redefine a term used in the claims). And if the specification reveals "an intentional disclaimer, or disavowal, of claim scope by the inventor," the scope of the claim, "as expressed in the specification, is regarded as dispositive." *Phillips*, 415 F.3d at 1316 (citing *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1343–44 (Fed. Cir. 2001)).

Disclaiming the ordinary meaning of a claim term—and thus, in effect, redefining it—can be affected through "repeated and definitive remarks in the written description." *Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1374 (Fed. Cir. 2008) (citing *Watts v. XL Sys.*, 232 F.3d 877, 882 (Fed. Cir. 2000)); *see SafeTCare Mfg., Inc. v. Tele-Made, Inc.*, 497 F.3d 1262, 1270 (Fed. Cir. 2007) (finding disclaimer of "pulling force" where "the written description repeatedly emphasized that the motor of the patented invention applied a pushing force"); *SciMed*, 242 F.3d at 1344 ("[T]he written description can provide guidance as to the meaning of the claims, thereby dictating the manner in which the claims are to be construed, even if the guidance is not provided in explicit definitional format."); *Bell Atl. Network Servs., Inc. v. Covad Commc'ns Grp., Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001) ("[A] claim term may be clearly redefined without an explicit statement of redefinition. . . . In other words, the specification may define claim terms by implication such that the meaning may be found in or ascertained by a reading of the patent documents." (citations omitted) (internal quotation marks omitted)); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) ("The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication."). We do, though, "recognize that the distinction between using the specification to interpret the meaning of a claim and importing limitations from the specification into the claim can be a diffi-

cult one to apply in practice." *Phillips*, 415 F.3d at 1323. However, we can rely on the specification "to understand what the patentee has claimed and disclaimed." *SafeTCare Mfg.*, 497 F.3d at 1270.

B. Analysis

The district court found that "the inventors defined 'culturing . . . cells in three-dimensions' by implication to exclude culturing on beads," even though "culturing cells in three dimensions on beads was known in the art at the time the patent was filed." J.A. 50. We agree with the court's exclusion of beads from the construction of the disputed phrase. In the written description, the patentees plainly and repeatedly distinguished culturing with beads from culturing in three-dimensions. They expressly defined the use of beads as culturing in two-dimensions. And they avoided anticipatory prior art during prosecution by asserting that the conditioned medium produced by two-dimensional cultures was inferior and chemically distinct from the conditioned medium produced by three-dimensional cultures. Because none of the evidence called to our attention by SkinMedica would reasonably lead to a different reading of the intrinsic evidence, we find that the inventors clearly redefined the scope of "culturing . . . cells in three dimensions" by disclaiming the use of beads—which would otherwise be included in the ordinary meaning of that phrase.[6]

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[6] While Histogen appears to dispute on appeal whether the ordinary meaning of three-dimensional cell culture can include the use of beads, it appears to have conceded the point to the district court. Def.'s Responsive Claim Construction Br. 11, *SkinMedica v. Histogen*, No. 3:09-cv-122, (S.D. Cal. July 21, 2009), ECF No. 48 ("When the '494 patent application was filed, culturing three-dimensional tissues on beads was known in the art. . . .

1. The Intrinsic Record

The patentees refer to "beads" five times in the intrinsic record. All of those references appear in the written description, and four concern the use of beads in cell culturing.[7] In each and every one of those four references, the patentees clearly distinguish culturing with beads from culturing in three-dimensions.

a. Beads "as opposed to" Three-Dimensional Cultures

The patentees' first use of the term "beads" comes during their discussion of the characteristics of the cells grown by methods known in the art. In a subsection titled "Conditioned Cell Media" that appears in the background section of the written description, the patentees state:

> Conditioned medium contains many of the original components of the medium, as well as a variety of cellular metabolites and secreted proteins, including, for example, biologically active growth factors, inflammatory mediators and other extracellular proteins. *Cell lines grown as a monolayer or on beads, as opposed to cells grown in three-dimensions*, lack the cell-cell and cell-matrix interactions characteristic of whole tissue in vivo.

'494 patent col. 1 ll. 33–44 (emphasis added).

[T]he . . . inventors would have understood that beads could be used in three-dimensional culture systems.").

[7] The fifth reference to beads appears in a section of the written description discussing the use of "[r]igid spherical beads suspended in a Newtonian fluid" as part of "formulations for dermal augmentation." '494 patent col. 26 ll. 35-50. Neither of the parties contends that reference is somehow relevant here.

It is quite apparent from the use of the disjunctive phrase "as opposed to" that the patentees considered cells grown on beads to be different and distinct from cells grown in what they considered to be three-dimensions. The plain meaning of the disjunctive phrase, "as opposed to," is "contrary or opposite to" or "standing in opposition, contrast, or conflict." *Oxford English Dictionary* 867, vol. X (2d ed. 1989).

SkinMedica, however, would like to limit the import of the disjunctive phrase by reading the passage as: "Cell lines grown as a monolayer or 'on [*the surface of the*] beads,' as opposed to cells grown in three-dimensions." Appellant's Br. 38 (alteration in original) (emphasis added). The addition of the phrase "the surface of the" is necessary, according to SkinMedica, to clarify that "the text is addressing only two-dimensional culturing" with beads. *Id.* That clarification is important in SkinMedica's view because beads can be used to culture cells in both two- and three-dimensions, and the "specification's mentions of beads simply emphasize that beads can be used for purely 'two-dimensional' culturing (*i.e.*, a single layer of cells cultured on the surface of the beads) and when so used are not sufficient to practice the invention." *Id.*

We do not see any reason to add additional language to the passage—especially the phrase proposed by SkinMedica. The plain words selected by the inventors exhibit a clear intent to distinguish between three-dimensional culturing and culturing in monolayer and on beads. Nowhere do the inventors indicate otherwise. Nor at any point—in the written description or in the entire prosecution history—do the inventors ever mention the "surface" of beads. And there is no indication in the specification or prosecution history that the inventors believed beads could be used for both two- and three-dimensional culturing—as they used those terms in their patents. Rather, as the patentees stated to avoid prior art

during prosecution, "conditioned medium obtained from . . . cells cultured in two-dimensions . . . [is] not identical, *expressly or inherently*" to "medium obtained from the same cells cultured in three-dimensions." J.A. 101245–46 (emphasis added). The patentees clearly distinguished two-dimensional and three-dimensional cultures as distinct and different methods to culture cells with distinct and different results.

The plain import of the phrase "[c]ell-line grown as a monolayer or on beads, as opposed to cells grown in three-dimensions" is that, in context of the patents, cultures in which cells are grown on beads are distinct and different from cultures in which cells are grown in three-dimensions. In light of the specification and prosecution history, that means cells grown on beads are cells grown in a two-dimensional culture.

b. Beads Produce Inferior Cell Culture Medium

The second reference to beads made by the patentees immediately follows the first.

> Cell lines grown as a monolayer or on beads, as opposed to cells grown in three-dimensions, lack the cell-cell and cell-matrix interactions characteristic of whole tissue in vivo. Consequently, such cells secrete a variety of cellular metabolites although they do not necessarily secrete these metabolites and secreted proteins at levels that approach physiological levels. *Conventional conditioned cell culture medium, medium cultured by cell-lines grown as a monolayer or on beads, is usually discarded* or occasionally used in culture manipulations such as reducing cell densities.

'494 patent col. 1 ll. 33–44 (emphasis added).

In that passage, the inventors unmistakably differentiate culturing on beads from culturing in three-dimensions by distinguishing the chemical composition of

the medium conditioned by cells grown by each method. The patentees first mention why the "metabolites and secreted proteins" in medium conditioned by cells grown "as a monolayer or on beads" are different than those in medium conditioned by "cells grown in three-dimensions": because the latter have "cell-cell and cell-matrix interactions characteristic of whole tissue in vivo." *Id.* They then declare that the "conventional" medium conditioned by cells "grown as a monolayer or on beads" is "usually discarded." *Id.* There is a logical and plain conclusion from the passage. It is that "cell-lines grown as a monolayer or on beads" are distinct from three-dimensional cultures because they produce "conventional" media with inferior chemical compositions.

The prosecution history supports this conclusion. During prosecution of the '494 patent, the patentees juxtaposed the chemical composition of the medium produced by three-dimensional cultures with the medium produced by "conventional" means to demonstrate that the medium used in their patents was part of a novel and patentable invention. To overcome an anticipation rejection, the patentees argued that "[c]ulturing cells in three-dimensions results in the production of a conditioned medium *having a different chemical composition* than that of cells cultured by *conventional* means." J.A. 101245 (first emphasis altered) (second emphasis added). They also explained that the two media were "not identical, expressly or inherently" and differed, in part, by the abundance of growth factors and other cell metabolites. J.A. 101245–46; *see also* J.A. 101284-91 (a declaration submitted by patentees' expert during prosecution describing the differences between the media in specific detail).

In its briefing on appeal, SkinMedica even acknowledges that "a key advantage of culturing in three dimensions" is the chemical composition of the medium conditioned by cells grown in such cultures. They agree

with the district court that "cells cultured in three dimensions secrete growth factors and other proteins in [higher] ratios" and that the medium conditioned by them are accordingly "superior." Appellant's Br. 31 (internal quotation marks omitted).

We therefore read the second reference to beads in the written description as another clear and unmistakable statement that bead cultures are not the three-dimensional cultures the inventors require in their claimed methods.[8] The inventors argued during prosecution that the chemical composition of the medium produced by cells cultured in three-dimensions was a novel and patentable aspect of their invention (an argument with which SkinMedica agrees), and they clearly stated in the written description that cultures of cells grown on beads do not produce such novel and patentable results (they are "usually discarded"). Such emphasis on a particular mode of operation, especially to avoid prior art, can operate as a disclaimer of the otherwise broad scope of a claim term. *See SafeTCare Mfg., Inc. v. Tele-Made, Inc.*, 497 F.3d 1262, 1270 (Fed. Cir. 2007) (finding disclaimer when a feature was repeatedly emphasized in contradiction to another and that particular "attribute of the invention [was] important in distinguishing the invention over the prior art").

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[8] The only reason presented by SkinMedica to read the second reference to beads differently is because they believe that "the advantages of three-dimensional culturing apply equally to bead-based three-dimensional culturing." Appellant's Br. 31. That belief, however, is premised on Dr. Salomon's opinion, Doyle, and Seldon—evidence we find unpersuasive in light of the clear disclaimers in the written description. *See* discussion *infra* Section II(B)(2).

c. Beads (i.e., Two-Dimensions)

The third reference to beads made by the patentees occurs at the beginning of a section titled "Detailed Description of the Invention." It states that:

> The present invention relates to novel compositions comprising any conditioned defined or undefined medium, cultured using any eukaryotic cell type or three-dimensional tissue construct and methods for using the compositions. *The cells are cultured in monolayer, beads (i.e., two-dimensions) or, preferably, in three-dimensions.*

'494 patent col. 7 ll. 24–29 (emphasis added).

Here, the patentees once again list cell culture methods that can be used in their invention,[9] and once again, clearly differentiate between cells cultured using beads and those cultured in three-dimensions. They list methods for culturing cells, include beads and three-dimensions in that list, and use a disjunctive ("or") as the coordinating conjunction that reveals the relationship of the members in the list. The disjunctive "or" plainly designates that a series describes alternatives. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1331 (Fed. Cir. 2001) (explaining that "or" designates alternatives); *see also Oxford English Dictionary* 882, vol. X (2nd ed. 1989) (defining "or" as a particle "coordinating two (or more) words, phrases, or clauses, between which there is an alternative"). In *Thorner*, we recognized that the "use of two terms as alternatives" functions as a redefintion of a term if that redefinition is "so clear that it equates to an explicit one." 669 F.3d at 1368. The pa-

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[9] The "invention" referenced by the patentees here is that which they originally envisioned, one not restricted to use of conditioned medium formed by cells cultured in three-dimensions.

tentees' distinction between bead and three-dimensional cultures is that clear. They not only repeated such a disjunctive listing of culturing methods elsewhere in the specification, but also expressly chose to define beads as culturing in "two-dimensions"—a definition that places beads in stark contrast to another method immediately following it in the list, "three-dimensions." And, unlike in their first reference to beads, the inventors here do not distinguish cells "grown" in three-dimensions from cells "grown" "on" beads; they broadly distinguish cells "cultured in" three-dimensions from cells "cultured in . . . beads."

Furthermore, we agree with the district court that the "phrase 'beads (*i.e*, two-dimensions)' explicitly define[s] beads as a two-dimensional culture method, despite that culturing cells in three-dimensions on beads was known in the art." J.A. 22. A plain reading of that phrase indicates that the patentees considered beads a form of two-dimensional culturing that was not akin to the three-dimensional culturing used in their invention. In a specification, a patentee's "use of '*i.e.*' signals an intent to define the word to which it refers." *Edwards Lifesciences LLC v. Cook Inc.*, 582 F.3d 1322, 1334 (Fed. Cir. 2009); *see also Abbott Labs. v. Novopharm Ltd.*, 323 F.3d 1324, 1330 (Fed. Cir. 2003) (holding that a patentee "explicitly defined" a term by using "*i.e.*" followed by an explanatory phrase). The inventors also used the phrase "*i.e.*" elsewhere in the specification (twelve other times in total) to introduce an explanation or definition of a word or phrase. *See* '494 patent col. 1 l. 7; col. 7 l. 44; col. 8 l. 65; col. 10 l. 1; col. 15 l. 16; col. 18 l. 52; col. 19 l. 20; col. 20 l. 16; col. 22 l. 40; col. 26 l. 15; col. 27 l. 36; col. 30 l. 58. Based on the plain meaning of the term "*i.e.*" and the patentees' consistent use of it throughout the specification, there is no reason to believe that the inventors did not intend for the abbreviation to signal an intent to define the word it followed when they stated "[t]he cells are cultured in . . .

beads (*i.e.*, two-dimensions) or, preferably, in three-dimensions."

SkinMedica, however, argues that the inventors did not explicitly define beads as a two-dimensional culture method. It asserts that our cases indicate that the "mere use of '*i.e.*' does *not* act as an express definition or limitation" and "must be read in the context of the patent as a whole." Appellant's Br. 41. Read in context, SkinMedica believes that the phrase "beads (*i.e.*, two-dimensions)" merely represents the inventors' recognition of the ability to use beads in both two- and three-dimensional cultures. To SkinMedica, the phrase simply clarifies culturing beads in two-dimensions is different from culturing beads in three-dimensions. Any other reading, in SkinMedica's view, would be inconsistent with the ordinary meaning of three-dimensional cultures, which includes the use of beads.

We agree with SkinMedica that our reading of "beads (*i.e.*, two-dimensions)" is "inconsistent" with the ordinary meaning of three-dimensional culturing; but that result is inescapable in context of the entire specification. Read as a whole, the specification provides no distinction between culturing with beads in two- versus three-dimensions in the specification. We do not believe that the patentees used the phrase "beads (*i.e.*, two-dimensions)" to signal that beads "can" be a two-dimensional culturing method. That is a not a natural reading. The inventors go to great lengths (in over twenty-five columns of text in the specification) to explain dozens upon dozens of different ways to culture cells in three-dimensions, yet do not mention beads once in any of them. *See* '494 patent cols. 7–32. And in the only places where the inventors mention culturing with beads in the specification, they clearly distinguish such culturing from growing or culturing cells in three-dimensions. During prosecution, the patentees disclaimed medium conditioned by "conventional means" and taught in the written description that cells grown on

beads produce such "conventional" medium. Reading "beads (*i.e.*, two-dimensions)" as definitional comports with the plain language of the specification as a whole and the inventors clearly expressed intent to differentiate the use of beads from three-dimensional culturing. While that result might be "inconsistent" with the ordinary meaning of three-dimensional culturing, it is one that the intrinsic record here plainly demonstrates to be correct.

In addition, the import we assign to the term "*i.e.*" here aligns with our case law. We have held—as discussed above—that a "specification's use of '*i.e.*' signals an intent to define the word to which it refers." *Edwards Lifesciences*, 582 F.3d at 1334. As SkinMedica correctly points out, such use of "*i.e.*" is not absolute. It identifies several cases in which we did not give "*i.e.*" its plain meaning and import. But the reasoning of those cases does not apply here.

SkinMedica first points to *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358 (Fed. Cir. 2012). In that case, which concerned DVD technology, we were unconvinced that a patentee's use of the term "*i.e.*" clearly expressed an intent to define a term and affect a prosecution history disclaimer. A patentee had responded to an office action and when describing a figure had stated: "As illustrated in FIG. 2 . . . [disc number and side] information must be provided on each side of the disc—*i.e., each recording plane*—in order for the disc side identifier 3 to serve its purpose of identifying which side is being recorded/reproduced." *Id.* at 1370 (emphasis added). We reasoned that the patentee's statement did not limit the claim term "recording plane" to a "disc side." *Id.* That was because the patentee was "merely explaining that, in the example in figure 2, a side of the disc constitutes a recording plane"—which did not mean "a recording plane is to be equated with a disc side in all instances." *Id.*

In contrast, the patentees here did not use the term "*i.e.*" to discuss how an aspect of one particular embodiment of their invention depicted in a figure satisfied a claim limitation. They were providing a list of different alternative methods by which cells could be cultured, and they used the term "*i.e.*" to describe how one of those methods *did not satisfy* a claim limitation. And, unlike in *Toshiba*, the definition that follows "*i.e.*" here directly *contrasts* the term it is defining with another listed alternative (two- versus three-dimensions).

Moreover, we are not assigning definitional intent to "*i.e.*" in order to directly assign meaning to a claim term. "Two-dimensions" appears nowhere in the allowed claims. And we are not proposing that the definition of "two-dimensions" (the term that follows "*i.e.*" here) be restricted to or defined as only "beads" (the word that precedes "*i.e.*"). We do the opposite: we read "beads" (the word that precedes "*i.e.*") to be defined by "two-dimensions" (the term that follows "*i.e.*"). That is a natural interpretation of "*i.e.*"

The other cases SkinMedica relies on are similarly distinguishable. In *Dealertrack, Inc. v. Huber*, we refused to read "*i.e.*" as showing intent to define because doing so would exclude multiple embodiments clearly discussed throughout the claims. 674 F.3d 1315, 1326 (Fed. Cir. 2012) ("The only way that the "*i.e.*" in this patent could be read definitionally is if it excluded from the claim scope the embodiments discussed throughout the claim where only a single funding source is selected. This is rarely, if ever, correct." (internal quotation marks omitted)). Here, the use of beads is mentioned nowhere in the claims. And in *Pfizer, Inc. v. Teva Pharmaceuticals, USA, Inc.*, we refused to limit a disputed claim term to a narrow definition introduced by "*i.e.*" in a patent specification because the specification expressly included a broader definition of the term in a different section that the "patentee clearly intended . . . to address the meaning of the same term."

429 F.3d 1364, 1373 (Fed. Cir. 2005). Here, there is no other section of the specification in which the patentees have defined "beads" as being broader than "two-dimensions."

Thus, we give the term "*i.e.*" here its plain meaning—that it "signals an intent to define the word to which it refers." *Edwards Lifesciences*, 582 F.3d at 1334. That reading comports with the inventors' other uses of the abbreviation in the specification and with each and every other reference to culturing with beads. We therefore conclude that the patentees expressly defined culturing in beads as a two-dimensional culturing method. Because it is defined as two-dimensional, culturing in beads cannot be the three-dimensional culturing required by the claims.

d. Cells Cultured in Beads or in Three-Dimensions

The fourth reference to beads made by the patentees occurs in the same section as the third, "Detailed Description of the Invention," but under the subheading, "The Cell Cultures." There the patentees state:

> The cells may be cultured in any manner known in the art including in monolayer, beads or in three-dimensions and by any means . . . .

'494 patent col. 9 ll. 66–col. 10 l. 1.

Once again, the patentees list cell culture methods that can be used in their originally-claimed invention, and again use the disjunctive "or" to differentiate between cells cultured using beads and those cultured in three-dimensions. As we concluded from such evidence previously, the use of the disjunctive in context of the entire specification and prosecution history in evidence plainly evinces an intent of the inventors to classify culturing with beads as a non-three-dimensional cell culturing method.

e. Conclusion From the Intrinsic Record

In sum, although the inventors never explicitly redefined three-dimensional cultures to exclude the use of beads, their implicit disclaimer of culturing with beads here was even "so clear that it equates to an explicit one." *Thorner*, 669 F.3d at 1368. Without fail, each time the inventors referenced culturing with beads in the specification, they unambiguously distinguished that culture method from culturing in three-dimensions. Every time they included beads in a list of methods for culturing cells, the inventors indicated that bead cultures were an alternative to three-dimensional cultures (by using the disjunctive "or") or distinct from three-dimensional cultures (by using the disjunctive phrase "as opposed to"). The inventors also discussed beads in order to explain how the conditioned medium created from cells grown in three-dimensions was chemically distinct and superior to the conventional conditioned medium created from cells grown on beads—a point of novelty the patentees relied upon during prosecution to avoid anticipatory prior art. And the patentees expressly defined culturing in beads as culturing cells in "two-dimensions," which excludes that method from the three-dimensional culturing required by the claims. The patentees repeated and definitive statements clearly indicate that they disclaimed the ordinary meaning of "culturing . . . cells in three-dimensions." *See, e.g.*, *Computer Docking Station Corp.*, 519 F.3d at 1374 (citing *Watts*, 232 F.3d at 882) ("[R]epeated and definitive remarks in the written description could restrict a claim limitation to a particular structure."); *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1117 (Fed. Cir. 2004) ("All that is required is that the patent applicant set out the different meaning in the specification in a manner sufficient to give one of ordinary skill in the art notice of the change from ordinary meaning. Because the inquiry into the meaning of claim terms is an objective one, a patentee who notifies the public that

claim terms are to be limited beyond their ordinary meaning to one of skill in the art will be bound by that notification, even where it may have been unintended."); *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) ("Where an inventor chooses to be his own lexicographer and to give terms uncommon meanings, he must set out his uncommon definition in some manner within the patent disclosure so as to give one of ordinary skill in the art notice of the change." (internal quotation marks omitted)); *see also Philips*, 415 F.3d at 1312 ("reaffirm[ing] the "basic principles of claim construction outlined" in several cases, including *Innova/Pure Water*).

Our holding comports with our cases in which we have found similar implicit disclaimers. For example, in *Bell Atlantic*, a patent holder argued for a plain meaning of the word "mode," which would "encompass[] different methods of altering . . . transmission *rates*." 262 F.3d at 1269 (emphasis added). We held, however, that the patentees redefined the broad term "mode" and excluded "rates" by "implication." *Id.* at 1273. Even though the patentees did not provide an "explicit definition[]" of "mode" that excluded "rates," we explained that they used "the claim term 'throughout the entire patent specification, in a manner consistent with only a single meaning,' one that was a 'different and distinct concept[]' than 'rate.'" *Id.* at 1271 (quoting *SciMed*, 242 F.3d at 1344 and *Vitronics*, 90 F.3d at 1582). As we found, the patentees had consistently described transmission "mode" and transmission "rate" as possessing different characteristics and had distinguished between them repeatedly by explaining that either transmission "rate *or* mode" could be independently altered. *Id.* at 1271–73. Thus, because there was no "[v]aried use of [the] disputed term," we held that the repeated explicit differentiation between the terms constituted a disclaimer. *Id.* at 1273 (quoting and distinguishing *Johnson Worldwide Assocs. v. Zebco Corp.*,

175 F.3d 985, 992 (Fed. Cir. 1999)) (internal quotation marks omitted).

As in *Bell Atlantic*, the patentees in this case have, without express redefinition, disclaimed a potential embodiment from the ordinary scope of a claim term through clear, repeated, and consistent statements in the specification that describe how culturing with beads is different and distinct from culturing in three-dimensions. Like the *Bell Atlantic* inventors, the patentees here repeatedly used the disjunctive "or" in the specification to carve out a disclaimed embodiment ("beads") from the ordinary meaning of a broad term ("culturing in three-dimensions"). And like the *Bell Atlantic* inventors, they also describe how the characteristics of the disclaimed embodiment were different from those of the claimed feature (that culturing on beads produces chemically different and inferior conditioned medium).

Furthermore, the patentees here have done even more than the inventors in *Bell Atlantic* to distinguish their disclaimed embodiment from the ordinary scope of a claim term. In addition to the disjunctive "or," they used the unambiguous disjunctive phrase "as opposed to" when differentiating between bead and three-dimensional cultures. They also expressly defined culturing with beads as culturing cells in "two-dimensions"—a definition that plainly excludes culturing with beads from three-dimensional cultures.

Thus, the patentees here have affected an even clearer implicit redefinition of a term than the inventors in *Bell Atlantic*. We stated in *Thorner* that an "'implied redefinition must be so clear that it equates to an explicit one." 669 F.3d at 1368. The implicit redefinition here satisfies even that hurdle. We are left with "no question that the . . . patent specification uses the terms ["culturing with beads"] and ["culturing in three dimensions"] to

refer to two different and distinct concepts." *Bell Atlantic*, 262 F.3d at 1272.

We also reached a similar result in *SafeTCare*. 497 F.3d 1262. In that case, we held that an inventor of an adjustable hospital bed disclaimed the full scope of the phrase, "pushing force on said plurality of *deck sections*." 497 F.3d at 1270 (emphasis added). The patent holder had argued for a broad construction to cover any bed that adjusted through a directional force applied to a "deck section." *Id.* at 1268-69. However, because the patentee "repeatedly emphasize[d]" in the written description that "the patented invention applies a pushing force . . . against a *lift dog* [a support member]," *not the deck section*, we limited the scope of the asserted claim to a pulling force exerted on a *lift dog*. *Id.* at 1270 (emphasis added). We felt additional comfort in reaching that result because the patentee had distinguished "conventional" adjustable bed frames in the written description by explaining: "[E]ach of the shafts . . . of bed lift motors [in the invention] . . . apply pushing forces against their respective lift dogs . . . . This is *in contrast to conventional* bed frames in which lift motors exert a pulling force against the frame." *Id.* (emphasis added).

Like the *SafeTCare* inventors, the inventors here affected a disclaimer by repeatedly emphasizing in the written description that culturing with beads is a method of culturing distinct from three-dimensional culturing—a point we have discussed extensively above. As we were in *SafeTCare*, we are reassured here of that disclaimer because the inventors distinguished their invention over the prior art by clearly differentiating between the medium produced by culturing with conventional means and the medium produced by culturing in three-dimensions. They did that not only in the specification—as the patentees in *SafeTCare* did—but also during prosecution to overcome anticipation and obviousness rejections.

It is therefore clear from the intrinsic record that, although the inventors never explicitly redefined "culturing . . . cells in three-dimensions" to exclude the use beads, they affected a clear implicit disclaimer of culturing with beads from the scope of their claimed invention.

2. Further Arguments Raised by SkinMedica

SkinMedica asserts four additional reasons not to find a disclaimer of beads. First, it asserts that the inventors "expressly defin[ed] the term 'three-dimensional framework,'" which is "used in 'culturing . . . in three-dimensions," to be "broad enough to include a three-dimensional structure formed using beads." Appellant's Br. 26. Second, it stresses that the specification incorporated and referenced Doyle, "which expressly discusses the use of beads to culture cells in three dimensions." Appellant's Br. 26. Third, it claims that Seldon "expressly acknowledges that three-dimensional culturing with beads provides the same inherent advantages—i.e., mimicking an in vivo environment—as other three dimensional culturing." Reply Br. 30. And, fourth, it asserts that Dr. Salomon "testified without contradiction that skilled practitioners understood that three-dimensional culturing could be performed using beads" and that "culturing using beads in three-dimensions produces the same benefits over two-dimensional culturing that the patents describe." Appellant's Br. 33. We take each argument in turn.

a. Three-Dimensional Framework

SkinMedica's first argument, that the patentees defined "three-dimensional framework" broadly enough to encompass the use of beads, is straightforward, but unhelpful. SkinMedica's argument is simple: "The inventors knew that beads could be used in three-dimensional culturing. Their definition of a three-dimensional framework broadly encompassed 'any material and/or shape.' Beads are of any material or shape. Therefore, the inven-

tors intended that beads could be used in three-dimensional culturing." *See* Appellant's Br. 25-26.

SkinMedica's theory misses the mark. It focuses on the three-dimensional framework being "any material and/or shape" and ignores that the inventors expressly restricted the definition of a "three-dimensional framework" to a "three-dimensional scaffold." The written description defines three-dimensional framework as:

> *[A] three-dimensional scaffold* composed of any material and/or shape that (a) allows cells to attach to it (or can be modified to allow cells to attach to it); and (b) allows cells to grow in more than one layer.

'494 patent col. 6 ll. 43–47 (emphasis added).

Beads obviously are "any material and/or shape," but that does not mean that they are also a "three-dimensional scaffold." Without explaining how beads are a "three-dimensional scaffold," SkinMedica's reliance on the definition of "three-dimensional framework" is incomplete. If we were to simply ignore the scaffold restriction, any structure of any material and/or shape that allows for cell attachment and for cell growth in more than one layer would be swept into the definition. That could not have been the inventors' understanding. For example, the patentees discuss in the written description that some "monolayer cultures . . . could grow to more than ten cells deep." *Id.* at col. 2 ll. 40–41. Without the scaffold restriction, the structure used to grow those types of monolayer cultures would meet the definition of a three-dimensional framework (cells attach and grow in more than one layer). *See id.* at col. 2 ll. 37–42. According to SkinMedica's theory, those cultures would therefore be three-dimensional. But no one contends that a monolayer culture should qualify as three-dimensional.

Because it is unclear how beads could be a three-dimensional scaffold, we are unconvinced by SkinMedica's argument that the inventors broadly defined "three-dimensional framework" to indicate their intent to include culturing with beads as a three-dimensional culturing method.

b. Doyle

According to SkinMedica, the inventors also could not have disclaimed the use of beads because they stated in the written description that "cells may be cultured in *any* manner known in the art" and incorporated Doyle into the specification,[10] which "expressly discusses the use of beads to culture cells in three dimensions." Appellant's Br. 26–30. In other words, according to SkinMedica, the inventors stated that any three-dimensional culturing method would work with their invention and listed culturing with beads as such a three-dimensional culturing method by incorporating Doyle. That argument fails for several reasons.

First, SkinMedica reads the phrase "cells may be cultured in any manner known in the art" out of context. The sentence from which SkinMedica plucked that phrase states that "[t]he cells may be cultured in any manner known in the art including in monolayer, beads or in three-dimensions and by any means." '494 patent col. 9 ll. 66–col. 10 l. 2. That statement described the scope of the invention covered by the original proposed claims, which were written to include *any* culture method. Those claims were rejected. The patentees restricted them to a single method of culturing—three-dimensional culturing—in order to avoid prior art. Therefore, while the *original proposed invention* could have used cells cultured in *any*

[10] The patentees stated in the written description that Doyle was "incorporated by reference . . . in [its] entirety." '494 patent col. 7 ll. 51-52.

manner known in the art, the *claimed invention* is limited to cells cultured *only in three-dimensions*. Accordingly, it is impossible to know whether any discussion of beads in Doyle was intended to be an example of the culturing methods covered by the broad original claims (which covered two- and three-dimensional cultures) or the narrow final claims (which was restricted to three-dimensional cultures).

Second, Doyle does not "expressly discuss[] the use of beads to culture cells in *three dimensions*," as claimed by SkinMedica. Appellant's Br. 26 (emphasis added). SkinMedica identifies one paragraph in that voluminous reference to support its assertion.

> A common occurrence in microcarrier culture is the formation of large microcarrier aggregates in which the microcarriers are joined by cellular bridges. Microcarrier aggregates made up of as many as 10 or more microcarriers are not uncommon. Microcarrier bridging occurs mainly during the growth phase of the culture, with little additional bridging occurring after cell growth has ceased (Borys & Papoutsakis 1992). This study also showed that there is an inverse relationship between the rate of microcarrier bridging and agitation intensity. Thus, it may be of interest to operate at higher agitation intensities during the growth phase of the culture to minimize microcarrier aggregation, and to slow down the agitation as cell growth slows to minimize cell detachment during the later stages of the culture. In certain cases, such as to promote bead-to-bead transfer of cells to bare microcarriers, low agitation rates would be desirable during the culture growth phase.

J.A. 100974. Nowhere does that portion of Doyle "expressly discuss" culturing with beads in "*three dimen-*

sions." The phrase "three dimensions" does not even appear in the passage.[11]

Third, even if we assume that the passage from Doyle discusses what one of ordinary skill in the art might understand to be three-dimensional culturing with beads, the inventors' general citation of Doyle does not indicate any reliance on that particular passage to define "culturing in three-dimensions" and to abandon the otherwise clear disclaimer of beads in the specification. When discussing cell culture methods, the patentees make the following reference to Doyle:

> The cells may be cultured in any manner known in the art including in monolayer, beads or in three-dimensions and by any means . . . . Methods of cell and tissue culturing are well known in the art, and are described, for example, in [Doyle], supra; Freshney (1987), Culture of Animal Cells: A Manual of Basic Techniques, infra.

'494 patent col. 10 ll. 2–6.

It is clear from that passage that the inventors did not refer to Doyle in order to define what they meant by "three-dimensional culturing" in their patent. They did not indicate their reference to Doyle was for that purpose; nor did they even refer with any detailed particularity to the passages in Doyle that, according to SkinMedica, may

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[11] Histogen's counsel stated at oral argument that Doyle does, in fact, reference culturing cells in three-dimensions. He asserted, however, that the reference is in the index and points readers to sections of the book that do *not* discuss culturing cells with beads. Oral Argument *available at* http://www.cafc.uscourts.gov/oral-argument-recordings/2012-1560/all 28:51-29:08. But the index of Doyle is not in the record. We therefore give no weight to counsel's statements.

have discussed three-dimensional culturing with beads. When the inventors wanted to use Doyle to explain the potential scope of terms they used, they did so specifically. *See* '494 patent col. 20 ll. 21–26 ("[I]t may be necessary to further process the resulting supernatant. Such processing may include . . . the methods described in [Doyle], *supra*, pp 29 D:0.1-29D:0.4."). But when describing cell culturing methods, the inventors generally referred to Doyle and another reference to support their assertion that many methods of cell culturing were well known in the art.[12] We see no reason for such a non-specific reference to trump the clear disclaimer in the specification of culturing with beads. *See Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (discussing how a host document must "identify with detailed particularity what specific material it incorporates" to properly incorporate such material by reference).[13]

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[12] That one of those methods known in the art could have been three-dimensional culturing with beads is of no import here. We assumed the patentees already knew that fact when we found a clear disclaimer in the specification.

[13] The district court relied on our decision in *Advanced Display Systems* to find that Doyle was not part of the intrinsic record because it was not incorporated with "detailed particularity." J.A. 22. SkinMedica argues that was error. Appellant's Br. 27-30.

It is unnecessary for us to decide whether Doyle was incorporated into the specification with adequate particularity to become part of the intrinsic record. We conclude that the inventors' reference to Doyle does not avoid a clear disclaimer of beads because it was not relied on by the inventors for an explicit or implicit definition of "culturing in three-dimensions" that included beads. The

Therefore, because Doyle does not define culturing with beads as "three-dimensional" and the inventors did not refer to Doyle for the purpose of defining what they meant by three-dimensional culturing, it does not inform our analysis in this case.

c. Seldon

SkinMedica argues that Seldon, an international patent application listed on the face of only the '746 patent, "expressly acknowledges that three-dimensional culturing with beads provides the same inherent advantages—i.e., mimicking an in vivo environment—as other three-dimensional culturing." Reply Br. 30. Specifically, SkinMedica asserts Seldon teaches that:

> Cells cultured in three dimensions using beads (i.e., cells that "formed attachments to both the bead surface and other cells" and "grew as bridges between . . . beads")—as opposed to "cells attached as monolayers" on "the bead's surface"—"were more reminiscent of that expected *in vivo*."

Reply Br. 30 (quoting Seldon).

At oral argument though, Histogen contended that SkinMedica's reliance on Seldon was improper because SkinMedica raised Seldon for the first time in its reply brief on appeal. Oral Argument *available at* http://www.cafc.uscourts.gov/oral-argument-recordings/2012-1560/all 26:36-50. We agree.

Advanced Display Systems detailed particularity requirement may, however, be a helpful framework for determining whether a patentee has clearly intended to rely on a portion of an incorporated document to effect or avoid a disclaimer. *Cf. Helmsderfer*, 527 F.3d at 1381. (discussing how patentees must "clearly express an intent" to disclaim the ordinary meaning of the words they use in a claim).

Clearly, Seldon is not part of the intrinsic record we consider for claim construction. It was listed on the face of the '746 patent as a reference cited during prosecution. But Seldon is not in evidence. It is not in the record on appeal and played no part in the proceedings below. Indeed, when referring to Seldon in its reply brief, SkinMedica could only cite to a publically available copy of the reference, not the record. *See* Reply Br. 30. Thus, Seldon is, at best, extrinsic evidence belatedly cited by SkinMedica in its reply brief.

Even as extrinsic evidence, though, we decline to consider Seldon. Seldon is a technically-dense patent application. It has a fifty-one page written description and twenty-four claims directed at "hepatocytes in three dimensional support systems." Seldon at 1. SkinMedica crafts a nuanced theory about cell culturing with beads by simply quoting a few short disjointed phrases from the lengthy reference. Yet it has provided no context for those quotes or any reasoning for its conclusions past the quotes themselves. And because it waited until its reply brief on appeal to first mention Seldon, neither the district court nor Histogen have had an opportunity to fully discuss the importance of the disclosures in the reference. "[E]xtrinsic evidence can shed useful light on the relevant art" during claim construction. *Phillips*, 415 F.3d 1317. However, SkinMedica's tardiness has so shaded what light Seldon may have shed on the relevant art here that we cannot fairly consider it. We simply cannot decipher the import of the reference without adequate context. SkinMedica has waived its ability to rely on the reference for claim construction purposes on appeal. *See Conoco Inc. v. Energy & Envtl. Int'l, L.C.,* 460 F.3d 1349, 1358-59 (Fed. Cir. 2006) ("[A] party may not introduce new claim construction arguments on appeal or alter the scope of the claim construction positions it took below."); *Harris Corp. v. Ericsson Inc.*, 417 F.3d 1241, 1251 (Fed. Cir. 2005) ("An

appellate court retains case-by-case discretion over whether to apply waiver.").

d. Dr. Salomon's Testimony

The district court afforded Dr. Salomon's testimony "no weight" after finding that it was "inconsistent with the intrinsic patent record." J.A. 23 n.5. SkinMedica, however, believes that Dr. Salomon's testimony is relevant because of two points to which he testified "without contradiction": (1) "skilled practitioners understood that three-dimensional culturing could be performed using beads" and (2) "culturing using beads in three-dimensions produces the same benefits over two-dimensional culturing that the patents describe—*i.e.*, 'exhibit[ing] cell-to-cell and cell-matrix interaction characteristic of whole tissue in vivo.'" Appellant's Br. 33 (quoting J.A. 101615); *see also* Reply Br. 31. We agree with the district court.

The first point from Dr. Salomon's testimony highlighted by SkinMedica—that culturing with beads in three-dimensions was known in the art—simply confirms an assumption we already made during our analysis of the intrinsic record. When we determined that the inventors disclaimed culturing with beads, we assumed that culturing with beads in three-dimensions was known in the art. Dr. Salomon's validation of our assumption is irrelevant.

Dr. Salomon's discussion of the benefits of culturing with beads is equally unhelpful here because it is conclusory and incomplete. SkinMedica asserts that Dr. Salomon testified that three-dimensional bead cultures can produce the same benefits of three-dimensional culturing described by the patents. To support that assertion, it points us to a single passage from Dr. Salomon's testimony. Appellant's Br. 33–34 (arguing that Dr. Salomon's testimony is extrinsic evidence to show that "ordinary meaning applies"); *see also* Reply Br. 31.

> Q. In your opinion, Dr. Salomon, do fibroblasts that are cultured in three-dimensions *on microcarriers or beads*, do they exhibit cell-to-cell and cell-matrix interactions characteristic of whole tissue in vivo.
>
> A. Yes.
>
> Q. And have you seen that?
>
> . . .
>
> A. Yes.
>
> Q. And is that—is your opinion about that functional definition applied to three-dimensional use of beads consistent with what we saw in the Doyle reference . . . ?
>
> A. Yes.

J.A. 101614–15 (emphasis added).

While it does appear from that passage that Dr. Salomon agreed that bead cultures can provide benefits similar to three-dimensional cultures, Dr. Salomon's testimony consists exclusively of three conclusory affirmations elicited by leading questions posed by SkinMedica's counsel. His testimony lacks any convincing detail explaining why or how cells in bead cultures exhibit the characteristics of whole tissue in vivo he claims they possess. Indeed, the patentees explained at length how the three-dimensional cultures used in their inventions have specific and valuable characteristics of tissue in vivo. For example, they described how their three-dimensional cultures can provide for: sustained long-term proliferation of cells; stimulation of cell growth and proliferation; provision of a greater surface area for protein attachment; regulation of cell differentiation; adequate spatial distribution of cellular elements; establishment of localized microenvironments; and greater potential for movement of migratory cells. *See* '494 patent col. 1 ll. 37–40; col. 11

ll. 20–53; col. 14 ll. 20–36; J.A. 101245. But Dr. Salomon does not explain how culturing with beads provides for any of those important characteristics. He even fails to explain how culturing with beads provides for the sustained long-term proliferation of cells, the key characteristic of three-dimensional cultures that the patentees identified as distinguishing their invention from prior art—in both the specification and prosecution history. *See* discussion *supra*, Section I(A). Dr. Salomon's one-word confirmations of directed conclusions in leading questions simply lack any helpful or informative detail regarding the benefits of culturing with beads.

Moreover, while SkinMedica believes Dr. Salomon's statements are "perfectly consistent with the intrinsic record," Appellant's Br. 34, they are not. The patentees plainly stated in the written description that: "Cell lines grown as a monolayer or *on beads*, as opposed to cells grown in three-dimensions, *lack* the cell-cell and cell-matrix interactions characteristic of whole tissue in vivo." '494 patent col. 1 ll. 37–40 (emphases added). Dr. Salomon, though, testified that "fibroblasts culture[ed] in three-dimensions *on microcarriers or beads*, . . . exhibit cell-to-cell and cell-matrix interactions characteristic of whole tissue in vivo." J.A. 101614–15 (emphasis added). As the district court found, Dr. Salomon's testimony is "inconsistent with the intrinsic patent record." J.A. 23 n.5.

In whole, Dr. Salomon's opinions are unhelpful to our analysis here. They are conclusory and incomplete; they lack any substantive explanation tied to the intrinsic record; and they appear to conflict with the plain language of the written description. Without a more detailed explanation of how Dr. Salomon formed his conclusions and why they conflict with the plain language of the specification, we must agree with the district court that

Dr. Salomon's testimony deserves no weight.[14] *See Phillips*, 415 F.3d at 1318 (discussing how expert testimony "can suffer from bias that is not present in intrinsic evidence," is "not useful" if based on "conclusory, unsupported assertions," and should be "discount[ed]" if "clearly at odds with . . . the written record of the patent"); *see also Bell Atl. Network Servs.*, 262 F.3d at 1269 ("[Extrinsic evidence] may not be used to vary, contradict, expand, or limit the claim language from how it is defined, even by implication, in the specification or file history."); *Vitronics*, 90 F.3d at 1584 ("[W]here the patent documents are unambiguous, expert testimony regarding the meaning of a claim is entitled to no weight.").

III. CONCLUSION

Based on the clear language of the specification and the statements made by the patentees during prosecution,

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[14] Dr. Salomon also discussed his view of the inventors' statements differentiating culturing with beads from three-dimensional cultures. He appears to have concluded that they were simply instructions to culture with beads in three-, not two-, dimensions. *See* J.A. 101613 (Dr. Salomon testifying that the inventors referenced beads to merely teach that if "you should grow [cells] using beads[,] . . . you needed to set up your conditions in the bead cultures to favor the formation of . . . three-dimensional cultures. If you didn't, you were actually going to end up growing in 2-D."). But that conclusion suffers the same problem as the points Dr. Salomon makes in the parts of his testimony relied upon by SkinMedica: he never fully explained *why* and *how* he arrived at his opinion. Nor did he explain how his conclusions accounted for the fact that the written description was originally drafted to support the use of both two- and three- dimensional cultures to condition the medium used in the patentees' inventions.

we hold that the inventors of the '494 and '796 patents disclaimed beads as a method to culture the cells that condition the medium used in their claimed inventions. We accordingly affirm the district court's construction of the term "culturing . . . cells in three-dimensions," common to all the assert claims, as "growing . . . cells in three dimensions (excluding growing in monolayers or on microcarrier beads)." Because the construction of that phrase is the only issue raised by SkinMedica on appeal, we affirm the district court's grant of summary judgment of noninfringement to Histogen.

AFFIRMED

United States Court of Appeals for the Federal Circuit

SKINMEDICA, INC.,
Plaintiff-Appellant,

v.

HISTOGEN INC., HISTOGEN AESTHETICS LLC, AND GAIL K. NAUGHTON,
Defendants-Appellees.

2012-1560

Appeal from the United States District Court for the Southern District of California in No. 09-CV-0122, Judge Janis L. Sammartino.

RADER, *Chief Judge,* dissenting.

There is a "heavy presumption" in favor of the ordinary meaning of claim language. *Bell Atl. Network Servs., Inc. v. Covad Commc'ns Grp., Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001). To overcome this presumption, the patentee must "clearly set forth" and "clearly redefine" a claim term away from its ordinary meaning. *Id.* The disavowal must be "unmistakable" and "unambiguous." *Dealertrack, Inc. v. Huber*, 674 F.3d 1315, 1322 (Fed. Cir. 2013). This standard is "exacting." *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1366 (Fed. Cir. 2012). In my judgment, the patentees did not disavow the ordinary meaning of "culturing . . . cells in three-

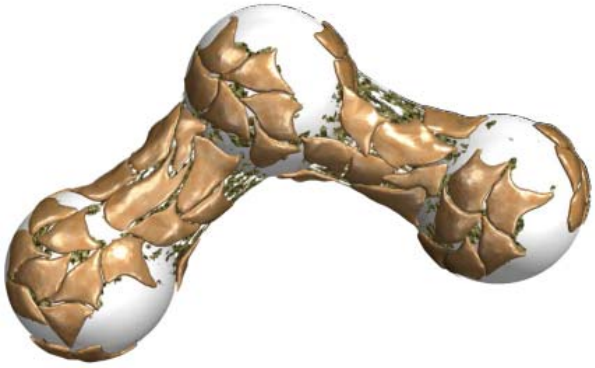
dimensions" to exclude the use of beads. Therefore, I respectfully dissent.

I.

Cells can be cultured on microcarrier beads in two-dimensions or in three-dimensions. Appellee's Br. 7–8. When cultured on beads in two-dimensions, the cells grow on the surface of each bead as single layer—or monolayer—of cells. J.A. 100972.

Appellant's Br. 7.

When cultured on beads in three-dimensions, the cells growing on the surface of one bead are allowed to connect with cells growing on the surface of another bead. This forms an interconnected structure having "cellular bridges" comprised of multiple layers of cells. J.A. 100974.



Appellant's Br. 7.

The district court found, and the parties do not dispute, that the ordinary meaning of "culturing . . . cells in

three-dimensions" includes the use of beads. J.A. 21. The district court held, however, that the patentees disavowed the ordinary meaning to exclude the use of beads, based on four references to beads in the patent specification. As described below, these references do not amount to an unmistakable and unambiguous disavowal.

II.

The first reference to beads appears in the "Background of the Invention" section of the specification:

> Conditioned medium contains many of the original components of the medium, as well as a variety of cellular metabolites and secreted proteins, including, for example, biologically active growth factors, inflammatory mediators and other extracellular proteins. *Cell lines grown as a monolayer or on beads, as opposed to cells grown in three-dimensions, lack the cell-cell and cell-matrix interactions characteristic of whole tissue in vivo.*

'494 patent col. 1 ll. 33–44 (emphasis added). In my view, the patentees used the disjunctive phrase "as opposed to" to distinguish "cells grown in three-dimensions" from cells grown "on beads" *in two-dimensions*.

The phrase "[c]ell lines grown as a monolayer or on beads" can reasonably be interpreted to mean cells cultured as a monolayer, or, as a monolayer on beads as described at the outset of this opinion. The parties do not dispute that cells cultured as a monolayer are inherently two-dimensional. *See* '494 patent col. 1 ll. 5–8.

Furthermore, the specification teaches that cells cultured "as a monolayer or on beads" are inferior to cells cultured in three-dimensions because they "lack the cell-cell and cell-matrix interactions characteristic of whole tissue in vivo." '494 patent col. 1 ll. 39–40. Uncontroverted extrinsic evidence shows that cells cultured in three-dimensions with beads have the same beneficial cell-cell

and cell-matrix interactions as cells cultured in three-dimensions without beads:

> Q. In your opinion, Dr. Salomon, do fibroblasts that are cultured in three-dimensions on microcarriers or beads, do they exhibit cell-to-cell and cell-matrix interactions characteristic of whole tissue in vivo.
>
> A. Yes.
>
> Q. And have you seen that?
>
> . . .
>
> A. Yes.
>
> Q. And is that—is your opinion about that functional definition applied to three-dimensional use of beads consistent with what we saw in the Doyle reference, the . . . Qiu reference and the other article?
>
> A. Yes.

J.A. 101614–15.

Dr. Salomon's testimony seems to confirm that the patentees' reference to cells grown "on beads" is in the context of two-dimensional cultures. Otherwise, it would not have made sense for the patentees to distinguish cells grown "on beads" from "cells grown in three-dimensions" because they have the same cell-cell and cell-matrix interactions characteristic of whole tissue in vivo.

The court recognizes this, but refuses to give Dr. Salomon's testimony any weight because it "consists exclusively of three conclusory affirmations elicited by leading questions posed by SkinMedica's counsel. His testimony lacks any convincing detail explaining why or how cells in bead cultures exhibit the characteristics of whole tissue in vivo he claims they possess." Majority Op. at 39–40. To my eyes, Dr. Salomon's testimony, when viewed as a whole, deserves great weight and respect.

Dr. Salomon testified extensively as to the nature of cells cultured on beads in both two-dimensions and three-dimensions. He discussed growth factors, cell proliferation, adhesion molecules, extracellular matrices, and gene expression, and "show[ed] you how you can do the same things with beads but now get three-dimensional growth." J.A. 101546–55. Dr. Salomon's testimony also included a detailed animated presentation and references to "a very well-known text-book to [persons of skill] in the field." J.A. 101553–55.

Much of Dr. Salomon's testimony does not appear in the parties' joint appendix because the extent of Dr. Salmon's testimony was not an issue in front of the district court. Dr. Salomon's testimony—including his assertion that cells cultured in three-dimensions with beads have the same beneficial cell-cell and cell-matrix interactions as cells cultured in three-dimensions without beads—was unrefuted. Histogen even conceded at oral argument that cells cultured in three-dimensions with beads have superior cell-cell and cell-matrix interactions compared to cells cultured in two-dimensions with beads. Oral Argument at 23:53, *available at* http://www.cafc.uscourts.gov/oral-argument-recordings/2012-1560/all.

The reason the district court refused to consider Dr. Salomon's testimony was because it "is inconsistent with the intrinsic patent record . . . ." J.A. 23 n. 5. This court agrees and states:

> The patentees plainly stated in the written description that: "Cell lines grown as a monolayer or *on beads*, as opposed to cells grown in three-dimensions, *lack* the cell-cell and cell-matrix interactions characteristic of whole tissue in vivo." Dr. Salomon, though, testified that "fibroblasts culture[ed] in three-dimensions *on microcarriers or beads*, . . . exhibit cell-to-cell and cell-matrix interactions characteristic of whole tissue in vivo." As the district court found, Dr. Salomon's testi-

> mony is "inconsistent with the intrinsic patent record."

Majority Op. at 41 (emphases original) (citations omitted). However, this conclusion only highlights the issue: whether or not the patentees' reference to "on beads" is in the context of two-dimensional cultures. If so, then Dr. Salomon's testimony is entirely consistent with the intrinsic patent record.

As to the leading nature of the questions posed by SkinMedica's counsel, Histogen did not object. Any defect as to the form of those questions has been waived. Fed. R. Civ. P. 32(d)(3)(B).

In sum, this reference to "on beads" is not a clear disavowal of "culturing . . . cells in three-dimensions." At a minimum, even absent Dr. Salomon's probative testimony, the specification is ambiguous. This court's precedent requires more.

III.

The second reference to beads immediately follows the first and is part of the same discussion:

> Cell lines grown as a monolayer or on beads, as opposed to cells grown in three-dimensions, lack the cell-cell and cell-matrix interactions characteristic of whole tissue in vivo. Consequently, such cells secrete a variety of cellular metabolites although they do not necessarily secrete these metabolites and secreted proteins at levels that approach physiological levels. *Conventional conditioned cell culture medium, medium cultured by cell-lines grown as a monolayer or on beads, is usually discarded* or occasionally used in culture manipulations such as reducing cell densities.

'494 patent col. 1 ll. 33–44 (emphasis added). This reference to beads is not a clear disavowal for the same reasons noted above.

This reference merely states that the medium resulting from cells grown "as a monolayer or on beads" do not secrete cellular metabolites and proteins at levels that approach physiological levels. However, as mentioned above, cells cultured in three-dimensions using beads have the same beneficial cell-cell and cell-matrix interactions as cells cultured in three-dimensions without beads. Thus, the resulting mediums would contain the same levels of metabolites and proteins. It would not make sense for the patentees to distinguish the medium resulting from cells cultured "on beads" from that of cells cultured in three-dimensions unless "on beads" is in the context of two-dimensional culturing.

IV.

The third reference to beads is in the section titled "Detailed Description of the Invention":

> The present invention relates to novel compositions comprising any conditioned defined or undefined medium, cultured using any eukaryotic cell type or three-dimensional tissue construct and methods for using the compositions. *The cells are cultured in monolayer, beads (i.e., two-dimensions) or, preferably, in three-dimensions.*

'494 patent col. 7 ll. 24–29 (emphasis added). This reference to beads is not an unmistakable and unambiguous disavowal.

The abbreviation "*i.e.*" is commonly used as a qualifier, meaning "that is to say" or "in other words." That is consistent with how the patentees used "*i.e.*" in other parts of the specification. *Contra* Majority Op. at 22; *see*, *e.g.*, '494 patent col. 15 ll. 15–19. It is reasonable to view the "*i.e.*" in this case as merely clarifying that the reference to beads is in the context of two-dimensions. The ambiguity is readily apparent. Nonetheless this court, without well-grounded reasoning, concludes that the patentees used "*i.e.*" to redefine beads as something other

than the plain and ordinary meaning as understood by those skilled in the art. Majority Op. at 20–26.

V.

The fourth reference to beads also occurs in the section titled "Detailed Description of the Invention":

> The cells may be cultured in any manner known in the art including in monolayer, beads or in three-dimensions and by any means . . . . Methods of cell and tissue culturing are well known in the art . . . ."

'494 patent col. 9 ll. 66–col. 10 l. 3. Again, because culturing cells using beads in both two-dimensions and three-dimensions was well-known in the art, I do not find a clear and unmistakable disavowal merely because the patentees used "the disjunctive 'or' to differentiate between cells cultured using beads and those cultured in three-dimensions." Majority Op. at 26.

VI.

In sum, to my eyes, the four references to beads relied on by this court are ambiguous. They do not meet the exacting standard imposed by this court's precedent. Because I would find that the patentees did not unmistakably and unambiguously disavow the ordinary meaning of "culturing . . . cells in three-dimensions" to exclude the use of beads, I would reverse the district court's grant of summary judgment.