United States Court of Appeals for the Federal Circuit

MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CHILDREN'S MEDICAL CENTER CORPORATION,
Plaintiffs-Appellees

v.

SHIRE PHARMACEUTICALS, INC., NKA SHIRE PHARMACEUTICALS LLC, SHIRE REGENERATIVE MEDICINE, INC.,
Defendants-Appellants

2015-1881

Appeal from the United States District Court for the District of Massachusetts in No. 1:13-cv-10020-MLW, Chief Judge Mark L. Wolf.

Decided: October 13, 2016

DARYL L. WIESEN, Goodwin Procter LLP, Boston, MA, argued for plaintiffs-appellees. Also represented by KEVIN PAUL MARTIN.

SANDRA KUZMICH, Frommer Lawrence & Haug LLP, New York, NY, argued for defendants-appellants. Also represented by EDGAR HAUG, LAURA ANN FANELLI, RUSSELL ALAN GARMAN, JONATHAN HERSTOFF.

Before O'MALLEY, CHEN, and STOLL, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* STOLL.

Concurring opinion filed by *Circuit Judge* O'MALLEY.

STOLL, *Circuit Judge*.

Massachusetts Institute of Technology and Children's Medical Center Corporation (collectively, "MIT") brought suit against Shire Pharmaceuticals, Inc. and Shire Regenerative Medicine, Inc. (collectively, "Shire") for infringement of U.S. Patent Nos. 5,770,193 and 5,759,830. The '193 and '830 patents are directed to three-dimensional scaffolding for growing cells in vitro to produce organ tissue in vivo. Following the district court's construction of the terms "vascularized organ tissue" and "cells derived from a vascularized tissue" and its determination that the term "three-dimensional scaffold" was not indefinite, the parties stipulated to a final judgment of validity and infringement. For the reasons below, we affirm.

BACKGROUND

I.

In the field of organ transplantation, surgeons face the challenge of donor scarcity in addition to the technical complexity of transplanting whole or segmented organs into organ recipients. Given the limited availability of implantable organs, scientists have developed methods of growing artificial organ tissue in vitro[1] by seeding cells onto support structures, known as scaffolds or matrices. These scaffolds are engineered to allow cells to attach and

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[1] In vitro refers to an artificial environment outside of a living organism, such as a test tube or culture. In vivo means within a living body.

grow, while enabling the diffusion of vital cell nutrients to the cells to contribute to the growth of new functional tissue.

Before the inventions of the asserted patents, scientists created organ tissue with scaffolds made of either "permanent" synthetic polymers or biodegradable, non-synthetic materials like collagen. Preferably, these scaffolds eventually would be absorbed by the body, leaving behind the newly formed tissue. With the former method, however, the "permanent" synthetic matrix could not be absorbed by the body. Drawbacks of the latter collagen-based matrix included the inability to control the collagen structure's configuration and the variable absorption of the collagen matrix by the surrounding tissue.

It was also generally understood that in engineering thick organs, like a liver or pancreas, the cells at the center of the artificial structure tended to die as the cell density increased. This was due to the decreased diffusion rate of oxygen and nutrients to the inner cells at the center of the growing structure. These prior art methods of tissue engineering, therefore, were primarily used to make thinner organs such as artificial skin.

In the face of these challenges, the inventors of the '193 and '830 patents, Drs. Vacanti and Langer, developed biodegradable, synthetic matrices that provide support for cell growth and enhance the formation of blood vessels (i.e., vascularization) of the growing cell mass after implantation. The specifications of the '193 and '830 patents state that "[t]he design and construction of the scaffolding is of primary importance," and that the scaffolding must be "shaped to maximize surface area to allow adequate diffusion of nutrients and growth factors to the cells." '193 patent col. 6 ll. 25–27; '830 patent col. 10 ll. 12–15. While the prior art methods were generally used to grow only artificial skin, the scaffolding of the claimed invention can support the growth of organs with varying thick-

nesses. Indeed, the specifications describe that an object of the invention is to "provid[e] a variety of organs, including skin, liver, kidneys, blood vessels, nerves, and muscles which functionally resemble the naturally occurring organ." '193 patent col. 3 ll. 9–13.

II.

The '193 and '830 patents claim three-dimensional, synthetic, biodegradable structures for growing tissue for vascularized organs as well as methods for creating those structures. MIT brought suit against Shire in the United States District Court for the District of Massachusetts, alleging that Shire's sale of its Dermagraft® scaffold infringes claims 1–4, 6–9, and 15–16 of the '193 patent and claims 1–4, 6, and 8 of the '830 patent. Claim 1 of the '830 patent is illustrative and recites the following, with emphasis given to the disputed terms:

> 1. A cell-scaffold composition prepared in vitro for growing cells to produce functional *vascularized organ tissue* in vivo, comprising:
>
> a fibrous *three-dimensional scaffold* composed of fibers of a biocompatible, biodegradable, synthetic polymer; and
>
> *cells derived from a vascularized tissue* attached in vitro to the surface of the fibers of the scaffold uniformly throughout the scaffold;
>
> wherein the fibers of the scaffold provide sufficient surface area to permit attachment in vitro of an amount of the cells effective to produce the functional vascularized organ tissue in vivo;
>
> wherein the fibers of the scaffold are spaced apart such that the maximum distance over which diffusion of nutrients and gases must occur through a mass of cells attached to the fibers is between 100 and 300 microns; and

> wherein the diffusion provides free exchange of nutrients, gases and waste to and from the cells uniformly attached to the fibers of the scaffold and proliferating throughout the scaffold in an amount effective to maintain cell viability throughout the scaffold in the absence of vascularization.

'830 patent col. 24 ll. 23–46 (emphases added).

Shire's accused Dermagraft® scaffold uses a synthetic, bioabsorbable scaffold seeded with connective tissue cells called fibroblasts to grow the dermis (or inner) layer of skin for "the treatment of full-thickness diabetic foot ulcers." J.A. 1004. Product literature for Dermagraft® describes that "[d]uring the manufacturing process, the human fibroblasts are seeded onto a bioabsorbable polyglactin mesh scaffold." *Id.* After seeding onto the Dermagraft® scaffold, "[t]he fibroblasts proliferate to fill the interstices of this scaffold and secrete human dermal collagen, matrix proteins, growth factors and cytokines, to create a three-dimensional human dermal substitute containing metabolically active, living cells." *Id.* The fibroblasts attach to the top, bottom, and sides of the fibers of the mesh scaffolding that, after implantation, is gradually absorbed by the surrounding tissue. According to MIT, Shire uses a three-dimensional, synthetic, biodegradable scaffold to grow vascularized organ tissue and thus infringes the asserted claims of the '193 and '830 patents.

III.

The parties dispute whether prosecution history disclaimer applies to the asserted claims. In particular, Shire argues that prosecution disclaimers apply to the terms "vascularized organ tissue" and "cells derived from a vascularized tissue." Prosecution of the asserted patents began with their parent application, U.S. Application Serial No. 06/933,018, filed in 1986 and abandoned in 1989. The '193 patent, a continuation of the parent, and

the '830 patent, a continuation-in-part of the parent, both issued in 1998. During the intervening years, MIT's strategy shifted in response to the examiners' prior art rejections, and the claim language evolved over the course of prosecution.

As originally filed, the pending claims in the '018 application were directed to:

> [P]roviding a matrix formed of a biocompatible material, wherein said matrix is used to support cell growth in a nutrient solution, said matrix being configured to allow adequate diffusion of nutrients from the nutrient solution to all of the cells so as to maintain cell growth and proliferation to form a three dimensional cell-matrix structure.

J.A. 22231–32. An examiner rejected the '018 application's claims based on prior art that, according to the examiner, "shows a tissue culture method on a carrier as claimed." J.A. 22212. In 1988, during an examiner interview in response to the prior art rejection, MIT explained that the prior art was directed to skin substitutes. In particular, MIT described the prior art as "limited to extremely thin pieces of collagen matrix for use in preparing skin substitutes, which could not be used to create organ equivalents." J.A. 22234. This interview summary further explained that "although porous structures for implantation have been made in the past, the pores have not allowed adequate diffusion through the matrix material between the environment and the attached cells to support the growth and proliferation of cells on the interior of the matrix material unless the dimensions of the matrix were very small." J.A. 22238. At the same time, MIT sought to amend the claims to recite a "matrix having adequate surface area to provide surfaces of attachment for a cell suspension and a geometric configuration to uniformly support cell growth in a nutrient solution." J.A. 22231–32.

Dr. Vacanti, a co-inventor on the asserted patents, submitted a declaration in 1989 in support of allowance of the '018 application, explaining that the prior art methods relied on by the examiner to reject the claims were "limited to a very thin layer of cells, principally serving as skin substitutes." J.A. 22268. He described the "key difference" between the claims and prior art as "the design of a polymer scaffold which provides adequate sites for attachment and growth of enough cells to survive and function in vivo yet does not limit survival and growth of cells adjacent to the matrix surface as cells increase in number in vitro." *Id.* Dr. Vacanti further emphasized the "general applicability" of the invention, which may be "use[d] with different cell types." *Id.*

In response, the examiner maintained his rejections of the '018 application's claims over prior art disclosing skin substitutes, dismissing MIT's argument that "the claimed method is not a method for making very thin structures." J.A. 22313. The examiner explained that the "claims herein are not exclusive to methods involving only thick structures." *Id.* At that time, the claims did not include a thickness limitation and were directed to:

> An artificial matrix for controlled cell growth in a nutrient solution comprising: a biocompatible matrix configured to provide points of attachment for a cell suspension, said matrix being configured to uniformly support cell growth in a nutrient solution, having sufficient area to allow adequate diffusion of nutrients, elimination of waste, and adequate gas exchange from the nutrient solution to all of the cells such that, in the absence of a vascular network, sufficient cellular growth and differentiation can occur to form a three dimensional cell-matrix structure.

J.A. 8142–43.

In 1989, in response to these continued rejections, MIT amended the claims of the '018 application to limit the claims to scaffolds for growing "non-skin organ cells." J.A. 8142–43. Likewise, MIT amended the claims in the applications that ultimately issued as the '830 and '193 patents to claim, respectively, "[a] biodegradable polymeric support matrix for culturing non-skin organ cells" and "[a] method for preparing a biodegradable polymeric matrix that serves as a cell culture scaffolding for non-skin organ cells." J.A. 1866, 3735. The examiner rejected all the new claims in each application under 35 U.S.C. § 112, reasoning that the "non-skin" limitations constituted new matter that was not supported by the original patent application. For example, the examiner of the '193 patent application stated:

> Claim 1, newly amended, recites an invention that includes "non-skin" organ cells. There is no description or teachings of enablement in the present specification of "non-skin" organ cells, *per se*. Consequently, the present specification as filed fails to meet the requirements of 35 USC 112, first paragraph with respect to "non-skin" organ cells. The term "non-skin" in claim 1 is deemed to be new matter.

J.A. 3768 ('193 patent); *see also* J.A. 8166 (same rejection for '830 patent).

MIT then withdrew the "non-skin" amendments for the asserted patents. J.A. 2272–73, 3774–75, 8173–74. In doing so, MIT emphasized that "no one, prior to applicants, recognized that the free diffusion of nutrients and gases, as opposed to cells, in combination with structure and sufficient attachment sites for the number of cells required to replace lost function, was essential to the formation of an organ replacement." J.A. 3789.

MIT abandoned the '018 parent application and continued to prosecute the applications that ultimately

issued as the '193 and '830 patents. At the time, MIT's claims included a limitation directed to the thickness of the claimed cell mass. For example, claim 1 of the '193 patent recited "[a] method for preparing cell-matrix structures comprising: determining the thickness through which nutrients and oxygen can diffuse through an animal cell mass for attachment and survival of the cells throughout the cell mass, wherein the dimensions of the cell mass are greater than 300 microns." J.A. 1638. The examiner rejected the claims under 35 U.S.C. § 112, first paragraph, asserting that "[t]he original specification fails [to] contain adequate support for steps a) and b) of claim 1, and for dimensions of a cell mass of greater than 300 microns." J.A. 4795. MIT responded by pointing to support in the specification, stating:

> Skin is differentiated from organs at page 6 of the application [i.e., '193 patent col. 2 l. 64 – col. 3 l. 17], where it is noted that it is considered to be such a thin structure that one does not have the limitations as to free diffusion into the center of the tissue.
>
> . . . It is clear from the foregoing excerpts from the patent application that construction of matrices for implantation of cells forming organs (as opposed to skin) are intended; it is described that this is only a problem when the diffusion distance to the middle is greater than 200 to 300 microns; and that volumes of greater than two to three mm^3 are intended to be implanted.

J.A. 1645. In that same office action response, MIT distinguished prior art "directed to formation of a skin substitute" on the ground that the prior art structure "has only been used to make relatively thin pieces of skin, not organ structures." J.A. 1653.

Later during prosecution, again in response to § 112 rejections of claims with the "greater than 300 microns" limitation, MIT stated:

> The specification identifies the problem to be solved as the need for structures replacing or supplementing tissue function, specifically pancreatic, liver, intestine, heart and skeletal or smooth muscle function (pages 2-5). The failure of the prior art to meet this need is reviewed at pages 5-6, noting that the prior art only exemplified skin replacement, not replacement of organs. . . . The objects of the invention recited at page 7 make clear that it is the formation of thick organ structures that is the primary goal of the invention.

J.A. 1709. Similarly, in the same office action response, Applicants discussed the prior art reference Yannas, which is directed to skin substitutes: "[B]ecause Yannas, et al. never makes a thick structure, they do not recognize the inherent limitation of their collagen gels which prevent making thick structures, which are essential for making organs but not for making skin replacements." J.A. 1716.

In 1997, when the examiners continued to reject the claims directed to a cell mass greater than 300 microns, MIT removed these thickness limitations from the claims and again shifted its prosecution strategy. Specifically, MIT cancelled the pending independent claims and added claims in both the '193 and '830 patents to require that the scaffold be used "to produce functional vascularized organ tissue *in vivo*." J.A. 4972, 9116. In an examiner interview summary, MIT explained that, "although the [prior art Yannas] lattice is uniquely suited for treating skin, it would be unsuitable for carrying out the goal of the claimed invention, especially when applied to vascularized organs, and structures that are thicker than skin." J.A. 9125. MIT further described Yannas as "suitable for

skin repair, or for regenerating nonvascular tissues." J.A. 9126. MIT asserted that Yannas could not, "without serious modification, be applied to the purposes of the presently claimed invention for producing *vascularized* tissues and organs." J.A. 9126–27. MIT also cited a report by Yannas himself, which stated that his matrix "supported regeneration of the epidermis (i.e., the outer *avascular* layer of skin) *on top* of the grafted lattices" but that it "induced only *partial regeneration of the dermis*—i.e., the *vascularized* component of skin." J.A. 9127. Following minor amendments, the '193 and '830 patents issued in 1998, claiming structures for growing cells to produce functional vascularized organ tissue and methods for creating those structures.

IV.

During claim construction proceedings in the district court, Shire argued that the term "vascularized organ tissue" should be construed to exclude skin as an organ based on various statements made during the prosecution of the asserted patents, discussed above. Shire made similar arguments regarding construction of the term "cells derived from a vascularized tissue," arguing that MIT had made statements during prosecution that limited the term to certain types of cells, namely parenchymal cells and bone forming cells. Shire further argued that the term "three-dimensional scaffold" was indefinite under 35 U.S.C. § 112. The district court, however, determined that prosecution history disclaimer did not apply and additionally held that the term "three-dimensional scaffold" was not indefinite.

Following the district court's claim construction and indefiniteness determinations, Shire stipulated to validity and infringement of the patents-in-suit and dismissed its declaratory judgment counterclaims of invalidity and noninfringement. The district court accordingly entered judgment of validity and infringement, and Shire ap-

pealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

Shire argues on appeal that the district court erred in construing the term "vascularized organ tissue" simply as "vascularized tissue from an organ" and in determining that the term "cells derived from a vascularized tissue" encompasses "at least some cells derived from skin." *See* J.A. 3–4. Shire also challenges the district court's determination that the term "three-dimensional" is not indefinite, as well as its construction of the term "three-dimensional scaffold" to mean "a supporting structure that allows cells to attach along its width, length, and height." J.A. 4. We address each claim limitation in turn below.

I.

The "ultimate interpretation" of a claim term, as well as interpretations of "evidence intrinsic to the patent (the patent claims and specifications, along with the patent's prosecution history)," are legal conclusions, reviewed by this court de novo. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). "Subsidiary factual determinations based on extrinsic evidence are reviewed for clear error." *Info–Hold, Inc. v. Applied Media Techs. Corp.*, 783 F.3d 1262, 1265 (Fed. Cir. 2015) (citing *Teva*, 135 S. Ct. at 841).

The purpose of claim construction is to give claim terms the meaning understood by a person of ordinary skill in the art at the time of invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–14 (Fed. Cir. 2005) (en banc). "There is a heavy presumption that claim terms are to be given their ordinary and customary meaning." *Aventis Pharm. Inc. v. Amino Chems. Ltd.*, 715 F.3d 1363, 1373 (Fed. Cir. 2013). "Properly viewed, the 'ordinary meaning' of a claim term is its meaning to the ordinary artisan

after reading the entire patent." *Phillips*, 415 F.3d at 1321. A patent's prosecution history, though "'less useful for claim construction purposes' than the claim language and written description, plays various roles in resolving uncertainties about claim scope." *SAS Inst., Inc. v. ComplementSoft, LLC*, 825 F.3d 1341, 1349 (Fed. Cir. 2016) (quoting *Phillips*, 415 F.3d at 1317). We recognize that "the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention." *Phillips,* 415 F.3d at 1317.

A.

"The doctrine of prosecution disclaimer . . . preclud[es] patentees from recapturing through claim interpretation specific meanings disclaimed during prosecution." *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003). "[I]n order for prosecution disclaimer to attach, the disavowal must be both clear and unmistakable." *3M Innovative Props. Co. v. Tredegar Corp.*, 725 F.3d 1315, 1325 (Fed. Cir. 2013). This case therefore requires that we analyze whether statements MIT made during the prosecution of the asserted patents amount to a clear and unmistakable disclaimer limiting the meaning of the claim terms. "Where the alleged disavowal is ambiguous, or even 'amenable to multiple reasonable interpretations,' we have declined to find prosecution disclaimer." *Avid Tech., Inc. v. Harmonic, Inc.*, 812 F.3d 1040, 1045 (Fed. Cir. 2016) (quoting *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1359 (Fed. Cir. 2003) and citing *Omega Eng'g*, 334 F.3d at 1325 ("[W]e have thus consistently rejected prosecution statements too vague or ambiguous to qualify as a disavowal of claim scope.")). "The party seeking to invoke prosecution history disclaimer bears the burden of proving the existence of a 'clear and unmistakable' disclaimer that would have been evident to one skilled in the art." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1063–64 (Fed. Cir. 2016).

B.

On the first term, "vascularized organ tissue," the district court determined that there was no clear and unmistakable disclaimer that would exclude skin from the term's ordinary meaning. The court therefore construed the term "vascularized organ tissue" according to its ordinary meaning as "vascularized tissue from an organ," reasoning that because "the dermal layer of skin contains blood vessels, this term encompasses skin." J.A. 3. We agree with the district court.

Shire does not dispute that the ordinary meaning of "organ" includes skin. Similarly, the ordinary meaning of "vascularized organ tissue" includes skin because skin contains vascularized layers, such as the dermis (or inner) layer. As MIT points out, the parties' Joint Technology Tutorial, provided to the district court as background during claim construction, expressly categorizes skin as an "organ," J.A. 3379, 3381, that is "vascularized," J.A. 3383–84.

The patents' respective specifications also support the district court's determination that the term "organ" includes skin. The specifications explicitly state that "[s]kin is an organ subject to damage by disease or injury" and that skin is "considered an 'organ' of the body." '193 patent col. 2 ll. 31, 64; *see also* '830 patent col. 4 ll. 8–9, 59. Moreover, the specifications state that "an object of the present invention" is "to provide a method and means for providing a variety of organs, *including skin*, liver, kidneys, blood vessels, nerves, and muscles which functionally resemble the naturally occurring organ." '193 patent col. 3 ll. 9–13 (emphasis added); *see also* '830 patent col. 5 ll. 10–14.

Shire nonetheless argues that skin should be excluded from the construction of "vascularized organ tissue" based on certain statements made by MIT during prosecution of the asserted patents' family. First, Shire pulls out a

single sentence from the 1988 interview summary prepared during prosecution of the parent '018 application, which stated that the asserted prior art "was limited to extremely thin pieces of collagen matrix for use in preparing skin substitutes, which could not be used to create organ equivalents." J.A. 22234. These statements, however, were made in the context of different claims that did not include the terms "vascularized organ tissue" or even "organ tissue." Rather, the claims were directed to "providing a matrix formed of a biocompatible material." J.A. 22231. Moreover, the interview summary particularly emphasized that "a crucial aspect of applicants' invention" is that the scaffold's structure allows "adequate diffusion through the matrix material between the environment and the attached cells to support the growth and proliferation of cells on the interior of the matrix." J.A. 22238. Reading the selected sentence in the context of the entire summary and the claim terms then at issue reveals that MIT emphasized the structure of the invention's scaffold, not the type of organ it can be used to grow.

Shire also points to Dr. Vacanti's 1989 declaration submitted during prosecution of the '018 application when the claims had been amended to require "determining the distance over which adequate nutrients and oxygen can diffuse through a cell mass having dimensions of greater than 200 microns to maintain viability of the cells on the interior of the cell mass." J.A. 2043. In particular, Shire relies on Dr. Vacanti's statement that, "[w]hile making skin equivalents does not require the use of thick layers of cells, making functional organs in vivo does." J.A. 22268. Review of the then-pending claims and Dr. Vacanti's declaration in full, however, reveals that he did not distinguish the claims from the prior art on the ground that organs do not include skin. Rather, Dr. Vacanti contrasted the prior art from the then-claimed invention on the ground that the prior art matrices cannot support "cells

[that] are grown to a thickness greater than the thickness which allows adequate diffusion of oxygen and nutrients to [the] inner cells." *Id.* Dr. Vacanti further explained that the claimed polymer matrices can be used "with different cell types," *id.*, and that, while his research focused on growing artificial livers, "a great strength of our approach is the generic application of knowledge to other organ systems." J.A. 22286. A skilled artisan would not read these statements in context as limiting the invention to any particular organ or as excluding skin.

Shire also points to Dr. Vacanti's statement that the prior art methods were "limited to a very thin layer of cells," whereas "the claimed method is not a method for making very thin structures." J.A. 22268, 2048. The declaration, however, was filed in support of claim limitations requiring a matrix of a minimum thickness. No such limitation is present in the issued claims. In determining whether a clear and unambiguous disclaimer attaches to particular claim language, it is important to consider the statements made by the applicant both in the context of the entire prosecution history and the then-pending claims. *See Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1342 (Fed. Cir. 2009) ("Even if an isolated statement appears to disclaim subject matter, the prosecution history as a whole may demonstrate that the patentee committed no clear and unmistakable disclaimer."). In the context of the overall prosecution history, the isolated statements plucked from Dr. Vacanti's declaration do not meet the high standard for prosecution disclaimer to attach.

MIT's attempt to add the "non-skin" limitation during prosecution of the asserted patents reinforces our conclusion that the asserted claims as issued include skin within their scope. MIT tried to narrow the application claims early in prosecution to exclude skin organ cells, but the examiner rejected the "non-skin" limitation under § 112 as new matter. MIT never again sought to limit the

claims to exclude skin organ cells. Had the examiner actually agreed with MIT's arguments and allowed the proposed amendments, the claims could well have a different claim scope. But the examiner did not, and MIT took a different approach. Since claims to "vascularized organ tissue" were ultimately allowed over the prior art without the proposed "non-skin" amendment, it is difficult to infer that a skilled artisan would interpret other isolated statements by MIT during the course of the prosecution history as a clear and unmistakable disclaimer of claim scope. Rather, we determine that a skilled artisan, reading the prosecution history as a whole, would conclude that MIT's invention does in fact cover vascularized skin.

Shire also points to a statement made by MIT during prosecution of a related but ultimately abandoned patent application. MIT stated there that "[t]he prior art describes the design of matrices for use as skin replacements, having different requirements than those of thick matrices required for organ function." J.A. 1913. The pending claims, however, required that the "dimensions of the cell mass are greater than 300 microns." J.A. 1972. Moreover, MIT described the pending claims as directed to "a method for the design and preparation of a matrix for the creation of thick organ equivalents." J.A. 1912. In context, Shire's reliance on MIT's statements is misplaced.

Shire similarly identifies statements made in 1995 during prosecution of the '193 patent to the effect that "construction of matrices for implantation of cells forming organs (as opposed to skin) are intended." J.A. 1645. Again, the pending claim language at that time included a thickness limitation, requiring that the "dimensions of the cell mass are greater than 300 microns." J.A. 1638. And these remarks were made in response to § 112 rejections in which the examiner stated that the original application lacks support for the thickness limitation. The full pas-

sage indicates that MIT was merely showing the examiner where the specification provided support for the claim limitation "greater than 300 microns":

> Adequate support means that one of ordinary skill in the art would be able to make and use the claimed invention. It is clear from the foregoing excerpts from the patent application that construction of matrices for implantation of cells forming organs (as opposed to skin) are intended; it is described that this is only a problem when the diffusion distance to the middle is greater than 200 to 300 microns; and that volumes of greater than two to three mm^3 are intended to be implanted.

J.A. 1645. MIT thus directed the examiner to written description support in the specification, which describes that "[a]lthough skin is considered to be an 'organ' of the body, these methods for making artificial skin have not been used to make other types of organs such as a liver or pancreas." '193 patent col. 2 ll. 64–66. MIT's remarks were made in the context of a thickness limitation not present in the issued claims and supported the notion that while the prior art was limited to creating artificial skin, the invention is capable of creating skin and also has a broader application. Moreover, several paragraphs later, the specification expressly states that an object of the invention is "to provide a method and means for providing a variety of organs, *including skin*." *Id.* col. 3 ll. 9–11 (emphasis added).

Finally, Shire points to MIT's statement that "the prior art only exemplified skin replacement, not replacement of organs." J.A. 1709. Again, this statement must be read in context. It was made when the claims included a thickness minimum, and MIT attempted to distinguish the claims on that basis, asserting that "it is the formation of thick organ structures that is the *primary* goal

of the invention." *Id.* (emphasis added). As such, MIT's statement cannot be read as limiting the ordinary meaning of "vascularized organ tissue" in the issued claims, which do not recite a thickness minimum.

We agree with the district court that Shire failed to meet its burden of demonstrating the existence of a "clear and unmistakable" disclaimer that would have been evident to one skilled in the art. *See Elbex Video, Ltd. v. Sensormatic Elecs. Corp.*, 508 F.3d 1366, 1371–72 (Fed. Cir. 2007). In the context of the entire prosecution history, the statements that Shire pulls out as alleged disclaimers, regarding claim limitations not present in the issued claims, do not alter or disclaim the ordinary meaning of "vascularized organ tissue" as used in the specification. We conclude that the district court properly determined that "vascularized organ tissue" includes skin as an organ.

C.

We also agree with the district court's construction of "cells derived from a vascularized tissue" to include both parenchymal and non-parenchymal (e.g., bone-forming) cells.

The claims themselves do not distinguish between parenchymal and non-parenchymal cells. Shire acknowledges that bone-forming cells, a type of non-parenchymal cell, fall within the claims' scope. Similarly, Shire's expert agrees that the ordinary meaning of "cells derived from a vascularized tissue" would "encompass both the parenchymal and non-parenchymal cells." J.A. 1320. In addition, several dependent claims expressly include organs with parenchymal and non-parenchymal cells. For example, claim 11 of the '193 patent lists smooth muscle cells, which are non-parenchymal stromal cells, not parenchymal cells.

Moreover, the respective specifications do not limit the term "cells derived from a vascularized tissue" to parenchymal cells, but instead use the term to also refer to several types of non-parenchymal stromal cells, namely cells forming smooth muscle and blood vessel endothelial cells. *E.g.*, '193 patent col. 4 ll. 6–16, col. 7 ll. 39–42; '830 patent col. 6 ll. 27–34, col. 7 ll. 51–56. Shire points out that the specifications "repeatedly refer to the cells of the invention as 'parenchymal,' 'functional,' or cells possessing the 'necessary' or 'desired' function." Appellant Br. 44. But Shire has not shown that these descriptions are synonymous, such that the invention should be limited to only parenchymal cells, especially in the face of the broad ordinary meaning of "cells derived from a vascularized tissue." And the specifications' reference to "an advantage of the present method" being "a means for selective transplantation of parenchymal cells" does not amount to a clear and unmistakable disclaimer restricting the claims to *only* parenchymal cells. '193 patent col. 5 ll. 56–58; *see also* '830 patent col. 9 ll. 14–18.

Finally, Shire pulls out statements from the prosecution of the '193 patent and a related patent that it argues disclaim non-parenchymal cells. The pending claims in these patent applications at the time of the statements, however, did not include the limitation in dispute—"cells derived from a vascularized tissue"—and do not clearly and unmistakably show that MIT intended to limit the claims at issue to only parenchymal cells.

For example, Shire quotes MIT's remarks made in response to a double patenting rejection during prosecution of the '193 patent. Specifically, MIT stated that "there are two major differences between what appellants are claiming and the claims" in Application No. 07/509,952 relating to cartilage, including "the requirement for chondrocytes rather than parenchymal cells." J.A. 1695–96. At the time of the double patenting rejection, the claims pending in the application that ultimately issued

as the '193 patent did not require the use of "cells derived from a vascularized tissue," and dependent claim 14 specifically recited cells forming cartilage (chondrocytes). J.A. 4672–74. In response to the double patenting rejection, MIT amended the '193 application claims to require the formation of "vascularized tissue" and removed claim 14's recitation of cartilage. The statements to which Shire points, therefore, simply distinguished the co-pending '952 application claims as being limited to cartilage, which is an avascular tissue. A skilled artisan would not read MIT's statements, which distinguish avascular cartilage from vascularized tissue made with parenchymal cells, as limiting the term "cells derived from a vascularized tissue" to parenchymal cells.

Shire also points to a statement made during prosecution of another related patent in the family, U.S. Patent No. 5,770,417, where MIT stated that "the types of cells described in the application are defined in Medical dictionaries and textbook[s] as 'parenchymal' cells." J.A. 1579. At that time, the application that ultimately issued as the '417 patent had claims directed to "cells selected from the group consisting of parenchymal cells from vascularized tissue and cells forming bone." J.A. 1598. This remark was made in response to an indefiniteness rejection, in which the examiner directed MIT to identify support in the specification for the disclosure of "parenchymal cells from vascularized tissue." MIT referenced the specification's list of types of cells, which included parenchymal cells as well as non-parenchymal stromal cells, in addition to general categories like intestine and kidney cells, which would include both parenchymal and non-parenchymal cells. MIT later shifted its prosecution strategy and removed the limitation of parenchymal cells in the claims, electing instead to require that the cells come from a vascularized tissue.

After reading the full prosecution history in light of the then-pending claim language, we conclude that a

skilled artisan would not read MIT's statement made during prosecution of the '417 patent—and directed to very different claim language—as limiting the term "cells derived from a vascularized tissue" to parenchymal cells. We, like the district court, determine that the ordinary meaning applies because Shire has not shown that a clear and unmistakable disclaimer attaches to limit the claim scope.

II.

Finally, Shire appeals the district court's determination that the term "three-dimensional scaffold" is not indefinite, as well as the court's ultimate construction of the term as "a supporting structure that allows cells to attach along its width, length, and height." J.A. 4. We affirm the district court's validity determination and adopt its claim construction.

"We review a district court's ultimate determination that a claim is invalid as indefinite under 35 U.S.C. § 112 ¶ 2 *de novo*, although, as with claim construction, any factual findings by the district court based on extrinsic evidence are reviewed for clear error." *UltimatePointer, L.L.C. v. Nintendo Co.*, 816 F.3d 816, 826 (Fed. Cir. 2016) (internal footnote omitted).[2] A claim is invalid for indefiniteness if its language, when read in light of the specification and the prosecution history, "fail[s] to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014). Patents are

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[2] Because the '193 and '830 patents were filed before the adoption of the Leahy–Smith America Invents Act, Pub. L. No. 112–29, § 4(e), 125 Stat. 284, 296-97 (2011), the previous version of § 112 governs. *See AbbVie Deutschland GmbH & Co. KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1290 n.3 (Fed. Cir. 2014).

presumed valid, and the challenger bears the burden of establishing invalidity. *See* 35 U.S.C. § 282; *Nautilus*, 134 S. Ct. at 2130 n.10.

Shire asserts that the term "three-dimensional scaffold" is indefinite because the intrinsic record provides "no guidance" as to the meaning of "three-dimensional." Appellant Br. 64. The district court rejected this argument and construed the term "three dimensional" according to its accepted, ordinary meaning, as confirmed by dictionary definitions. Shire complains that the dictionaries cited by the district court are from the present day and are not technical in nature. Yet Shire does not explain how technical dictionaries or dictionaries contemporaneous to the patents' filing date would define the term any differently. Moreover, the district court's construction is consistent with Shire's own expert's opinion regarding the term's ordinary meaning at the time of the invention:

> [A]t the time of the invention, . . . a POSA would have had some familiarity with the phrases "two-dimensional" and "three-dimensional" in the context of growing cells . . . . At that time a POSA would have understood the term "three-dimensional" as it relates to cell culture to refer to growing cells on and within a structure . . . . It is my understanding that a reference to three dimensions was an attempt to contrast this system (i.e., growing on and within) with the more traditional and widely-practiced "two-dimensional" conditions in which cells are grown in a single layer, usually on a flat, hard glass or plastic surface.

J.A. 1356.

Given the ordinary meaning of "three-dimensional" and Shire's own expert's description of "three-dimensional scaffold," we agree that the claim language is sufficiently definite under *Nautilus*. We likewise discern no error in

the district court's construction of "three-dimensional scaffold" to mean "a supporting structure that allows cells to attach along its width, length, and height." J.A. 4.

CONCLUSION

For the above reasons, we find no error in the district court's claim constructions of "vascularized organ tissue," "cells derived from a vascularized tissue," and "three-dimensional scaffold." We affirm its determination that the term "three-dimensional scaffold" is not indefinite. Accordingly, we affirm the district court's judgment.

AFFIRMED.

United States Court of Appeals for the Federal Circuit

MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CHILDREN'S MEDICAL CENTER CORPORATION,
Plaintiffs-Appellees

v.

SHIRE PHARMACEUTICALS, INC., NKA SHIRE PHARMACEUTICALS LLC, SHIRE REGENERATIVE MEDICINE, INC.,
Defendants-Appellants

2015-1881

Appeal from the United States District Court for the District of Massachusetts in No. 1:13-cv-10020-MLW, Chief Judge Mark L. Wolf.

O'MALLEY, *Circuit Judge*, concurring.

I agree with the majority that the district court did not err either in its construction of the disputed claim terms or in its conclusion that the term "three-dimensional scaffold" was not indefinite. Indeed, I believe the district court thoroughly and correctly analyzed all arguments and issues presented. I write separately, however, because I continue to believe that a judgment that is final except for a determination of damages and willfulness is not a final judgment at all.

DISCUSSION

The appellants assert that jurisdiction is proper because "[t]he judgment is 'final except for an accounting.'" Appellants' Br. 1 (quoting 28 U.S.C. § 1292(c)(2)). This is apparently so "because aside from MIT's request for (i) damages and (ii) a finding of willful infringement, the judgment disposes of all claims and counterclaims pending in the present case." *Id.*

In *Robert Bosch, LLC v. Pylon Manufacturing Corp.*, 719 F.3d 1305 (Fed. Cir. 2013) (en banc), we created a broad jurisdictional rule that excepts this court from the rules of finality followed by every other Article III court of appeals. We held that 28 U.S.C. § 1292(c)(2) "confers jurisdiction on this court to entertain appeals from patent infringement liability determinations when a trial on damages has not yet occurred" or "when willfulness issues are outstanding and remain undecided." *Id.* at 1317, 1319. And while I fully understand that § 1292(c)(2) is an exception to the final judgment rule that applies only to patent cases, I do not believe we should have strayed so far from the wise judgment of our sister courts. *See id.* at 1331 (O'Malley, J., dissenting) (collecting cases from other circuits holding that the finality requirement applies to outstanding damages determinations).

In declaring this broad, new rule in *Bosch*, we framed the question as "whether a trial on damages and willfulness is an accounting for the purposes of § 1292(c)(2)" and, therefore, an "exception[] to the final judgment rule." *Id.* at 1308. We answered that question by "conclud[ing] (albeit incorrectly in my view) that damages and willfulness determinations are sufficiently 'ministerial' to constitute no more than an 'accounting.'" *ePlus, Inc. v. Lawson Software, Inc.*, 789 F.3d 1349, 1371 (Fed. Cir. 2015) (O'Malley, J., dissenting). In so doing, we hammered a square peg into a round hole—these appeals are more

properly characterized as interlocutory and are, therefore, improper.

It is well established that "[t]he finality requirement . . . embodies a strong congressional policy against piecemeal reviews, and against obstructing or impeding an ongoing judicial proceeding by interlocutory appeals." *United States v. Nixon*, 418 U.S. 683, 690 (1974). Yet this court's continuing practice of allowing parties to appeal judgments where damages and willfulness remain undecided multiplies judicial proceedings by endorsing piecemeal review. *See Dow Chem. Co. v. Nova Chems. Corp. (Canada)*, 809 F.3d 1223, 1229 (Fed. Cir. 2015) ("[*Bosch*] authorized, nay encouraged, parties to engage in piecemeal appeals in patent cases and encouraged district judges to authorize the same.") (O'Malley, J., dissenting from denial of petition for rehearing en banc). This practice further incentivizes the disruption of district court proceedings by encouraging "district courts to bifurcate liability determinations from damages and willfulness trials—and all other remedial determinations," which will "drag out the litigation" in many cases, "causing multiple appeals and probably multiple remands." *Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 733 F.3d 1369, 1381 (Fed. Cir. 2013) (O'Malley, J., dissenting from denial of petition for rehearing en banc).

The final judgment rule is invaluable to ensuring the efficient and just resolution of patent disputes.

> The final judgment rule serves several important interests. It helps preserve the respect due trial judges by minimizing appellate-court interference with the numerous decisions they must make in the pre-judgment stages of litigation. It reduces the ability of litigants to harass opponents and to clog the courts through a succession of costly and time-consuming appeals. It is crucial to the efficient administration of justice.

Flanagan v. United States, 465 U.S. 259, 263–64 (1984). Exceptions to that rule are rare and disfavored. The Supreme Court has "repeatedly stressed," in the context of the collateral order doctrine, that a "'narrow' exception should stay that way and never be allowed to swallow the general rule that a party is entitled to a single appeal, to be deferred until final judgment has been entered, in which claims of district court error at any stage of the litigation may be ventilated." *Dig. Equip. Corp. v. Desktop Direct, Inc.*, 511 U.S. 863, 868 (1994). The increasing regularity of appeals taken under § 1292(c)(2), with damages and willfulness yet to be decided, demonstrates that the exception is indeed swallowing the general rule.

CONCLUSION

For these reasons, while I understand I am bound by it, I continue to believe that our decision in *Bosch* was in error. I concur in the result reached by the majority on the merits, but do not believe this court should continue its practice of exercising jurisdiction in cases where, as here, the district court has yet to determine damages and/or willfulness.