

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LASSEN THERAPEUTICS 1, INC.,
Petitioner,

v.

SINGAPORE HEALTH SERVICES PTE LTD., and NATIONAL
UNIVERSITY OF SINGAPORE
Patent Owner.

PGR2019-00053
Patent 10,106,603 B2

Before GEORGIANNA W. BRADEN, ROBERT A. POLLOCK, and
JAMIE T. WISZ, *Administrative Patent Judges*.

WISZ, *Administrative Patent Judge*.

DECISION
Denying Institution of Post-Grant Review
35 U.S.C. § 324

I. INTRODUCTION

Lassen Therapeutics 1, Inc. (“Petitioner”) filed a Petition (Paper 1, “Pet.”) requesting a post-grant review of claims 1–10 of U.S. Patent No. 10,106,603 B2 (Ex. 1001, “the ’603 patent”). Singapore Health Services PTE LTD. and National University of Singapore (“Patent Owner”) filed a Preliminary Response (Paper 8, “Prelim. Resp.”).

We have authority to determine whether to institute a post-grant review under 35 U.S.C. § 324 and 37 C.F.R. § 42.4(a). We may not institute a post-grant review unless “the information presented in the petition . . . , if such information is not rebutted, would demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” 35 U.S.C. § 324(a).

Applying that standard, and upon consideration of the information presented in the Petition and the Preliminary Response, we determine that the information presented fails to demonstrate it is more likely than not that at least 1 of the challenged claims of the ’603 patent is unpatentable. Accordingly, we deny institution of post-grant review of claims 1–10 of the ’603 patent.

A. Real Parties-in-Interest

Petitioner identifies itself, “Lassen Therapeutics 1, Inc.,” as the sole real party-in-interest. Pet. 1. Patent Owner identifies Singapore Health Services PTE LTD., National University of Singapore, Enleofen Bio Pte Ltd., Boehringer Ingelheim International GmbH, Boehringer Ingelheim USA Corporation, and Boehringer Ingelheim Pharmaceuticals, Inc., as the real parties-in-interest. Paper 9, 1.

B. Related Proceedings

Patent Owner indicates that the application from which the '603 patent issued is a Division of U.S. Patent Application No. 15/381,622 (U.S. Patent No. 10,035,852). Paper 9, 1. Patent Owner further indicates that the '603 patent claims priority to United Kingdom Application No. 1522186.4, to which a number of non-U.S. patent matters claim priority, including European Patent 3298040 B1 ("EP '040"). *Id.* at 2–3. Both parties indicate that an Opposition was filed against EP '040. Pet. 2; Paper 9, 3. Patent Owner also indicates that the following pending applications claim the benefit of priority of the filing date of the '603 patent: 16/055,245; 16/055,251; 16/055,261; 16/055,270; 16/055,283; 16/055,295; 16/055,304; 16/055,319; 16/106,041; 16/106,044; 16/106,047; and 16/106,050. Paper 9, 1

C. The '603 Patent

The '603 patent is directed to methods of treating fibrosis, including in humans. Ex. 1001, code (57), 1:14–15, 35:45–50. According to the '603 patent, fibrosis is the formation of excess fibrous connective tissue in a tissue or organ. *Id.* at 33:25–44. Fibrosis can occur in many tissues of the body including the liver, lungs, kidney, heart, blood vessels, eye, skin, pancreas, intestine, brain, and bone marrow. *Id.* at 34:10–13.

According to the '603 patent, the role of the protein Interleukin 11 ("IL-11") in fibrosis was not clear from the published literature; however, the inventors identified IL-11 to have a pro-fibrotic action and the patent provides *in vivo* data demonstrating IL-11 to be pro-fibrotic in heart, kidney, lung, and liver tissue. *Id.* at 1:51–52, 2:34–35, 45:54–46:2; Figures 21B–21C.

The '603 patent also describes methods of inhibiting or preventing the IL-11 mediated pro-fibrotic signal, e.g., as mediated by binding of IL-11 to an IL-11 receptor. *Id.* at 2:36–38. One disclosed method involves treating fibrosis by administering an Interleukin 11 receptor α (“IL-11R α ”) antibody capable of inhibiting signaling mediated by IL-11. *Id.* at 17:27–34. Such an antibody binds to the α component of a cell’s receptor for IL-11 and inhibits IL-11 from signaling via that receptor. *Id.* The '603 patent includes data showing that a neutralizing anti-IL-11R α antibody had an antifibrotic effect. *Id.* at 46:51–67; Fig. 24.

The '603 patent lists examples of known anti-IL-11R antibodies including “monoclonal antibody clone 025 (Sino Biological), clone EPR5446 (Abcam), clone 473143 (R & D Systems), clones 8E2 and 8E4 described in US 2014/0219919 A1 and the monoclonal antibodies described in Blanc et al (J. Immunol Methods. 2000 Jul. 31; 241(1–2); 43–59).” *Id.* at 18:41–46. The '603 patent teaches how to make new anti-IL-11R α antibodies by conventional immunization techniques and also describes the use of phage display. *Id.* at 50:40–51:18; 54:55–57:46.

D. Illustrative Claim

Petitioner challenges claims 1–10 of the '603 patent. Claim 1, which is the only independent claim of the '603 patent, is illustrative of the challenged claims, and is reproduced below:

1. A method of treating fibrosis in a human subject, the method comprising administering to the human subject in need of treatment a therapeutically effective amount of an Interleukin 11 receptor α (IL-11R α) antibody which is capable of inhibiting

Interleukin 11 (IL-11) mediated signaling, wherein the fibrosis is fibrosis of the heart, liver, kidney or eye.

Ex. 1001, 93:15–21.¹ Challenged claims 2–10 depend directly from claim 1.

E. The Asserted Grounds of Unpatentability

Petitioner contends claims 1–10 of the '603 patent are unpatentable in view of the following grounds. Pet. 3–4.

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–10	112(a)	Written Description
2	1–10	112(a)	Enablement
3	1–4, 6, 8–10	102	Edwards ²
4	1–10	103	Edwards
5	1–10	103	Edwards, Wynn ³ , Chegini ⁴

Petitioner submits the Declarations of Peter Bowers, Ph.D. (Ex. 1003) and Stephen Ledbetter, Ph.D. (Ex. 1004) in support of institution of post-grant review.

¹ The recited claim language incorporates the modifications from the Certificate of Correction issued on February 5, 2019. Ex. 1002, 1.

² Edwards et al., US 2014/0219919 A1, published Aug. 7, 2014 (Ex. 1008, “Edwards”).

³ Thomas A. Wynn, Fibrotic Disease and the T_{H1}/T_{H2} Paradigm, 4 Nat. Rev. Immunol., 583–594 (2004) (Ex. 1010, “Wynn”).

⁴ Chegini et al., US 2008/0300147 A1, published Dec. 4, 2008 (Ex. 1065, “Chegini”).

II. ELIGIBILITY FOR POST-GRANT REVIEW

The AIA’s post-grant review provisions apply to patents that “contain[] or contained at any time . . . a claim to a claimed invention that has an effective filing date . . . that is on or after [March 16, 2013].” Leahy-Smith America Invents Act (AIA) §§ 3(n)(1), 6(f)(2)(A) (2011). In addition, “[a] petition for a post-grant review may only be filed not later than the date that is 9 months after the date of the grant of the patent or of the issuance of a reissue patent (as the case may be).” 35 U.S.C. § 321(c) (2012); *see* 37 C.F.R. § 42.202(a) (2019).

Here, the ‘603 patent is eligible for post-grant review because the Petition was filed within nine months of the ‘603 patent’s issue date and the earliest possible priority date of the ‘603 patent is after March 16, 2013 (the effective date for the first inventor to file provisions of the Leahy-Smith America Invents Act). Ex. 1001, code (45) (showing an issue date of October 23, 2018); *id.* at 1:5–10 (claiming priority to a U.S. application and a United Kingdom application, the earliest of which was filed on December 16, 2015); *id.* at code (62), code (30); Paper 6 (according the Petition a filing date of July 23, 2019).

III. ANALYSIS

A. *Person of Ordinary Skill in the Art*

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Petitioner, relying on testimony of Dr. Bowers (Ex. 1003) and Dr. Ledbetter (Ex. 1004), contends that a person of ordinary skill in the art as of the relevant date would have been a person with:

a Ph.D. in immunology, molecular biology, cellular biology, or a similar field, or an M.D. with similar experience in one of the listed fields. [A person of ordinary skill in the art] would typically have had at least about five years of experience with antibodies and antibody engineering, or access to other individuals with that knowledge and experience. Likewise, a person of ordinary skill in the art would have had knowledge and experience in fibrosis, or access to a person with that knowledge and experience.

Pet. 13 (citing Ex. 1003 ¶ 113; Ex. 1004 ¶ 53) (citations omitted).

Patent Owner states that, for purposes of the preliminary response only, it does not challenge Petitioner's definition of a person of ordinary skill in the art. Prelim. Resp. 19. Based on the current record and for the purposes of this Decision, we adopt Petitioner's proposed description of the person of ordinary skill in the art. Furthermore, we find that the prior art of record reflects this level of skill in the art at the time of the invention. See *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

B. Claim Construction

Because this post-grant review is based on a petition filed after November 13, 2018,⁵ claim terms are construed using the same claim

⁵ On October 11, 2018, the USPTO revised its rules to harmonize the Board's claim construction standard with that used in civil actions under 35 U.S.C. § 282(b) in federal district courts. Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (now codified at 37 C.F.R. pt. 42 (2019)). This rule change applies to petitions filed on or after November 13, 2018.

construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.200(b) (2019). Under this claim construction standard, claim terms are given their ordinary and customary meaning as would have been understood by one of ordinary skill in the art at the time of the invention. *See id.*; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). A patentee may define a claim term in a manner that differs from its ordinary and customary meaning; however, any special definitions must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner provides proposed constructions for the terms “method of treating fibrosis,” “administering to the human subject in need of treatment a therapeutically effective amount,” “Interleukin 11 receptor α (IL-11R α) antibody,” “capable of inhibiting Interleukin 11 (IL-11) mediated signaling,” and “wherein the fibrosis is fibrosis of the heart, liver, kidney, or eye.” Pet. 5–13. Patent Owner disputes Petitioner’s construction of “Interleukin 11 receptor α (IL-11R α) antibody.” Prelim. Resp. 17–19. We discuss this term below.

1. “*Interleukin 11 receptor α (IL-11R α) antibody*”

Petitioner asserts that the term “Interleukin 11 receptor α (IL-11R α) antibody” should be construed as “any natural or synthetic, monoclonal or polyclonal antibody made using any animal system including phage, or fragment or derivative thereof that binds to IL-11R α of any species.” Pet. 10 (citing Ex. 1003 ¶ 108; Ex. 1004 ¶ 46). Petitioner asserts that nothing in the ’603 patent or its prosecution history limits the antibodies to human antibodies and, in fact, indicates that non-human antibodies are included by

explicitly mentioning that human antibodies are preferable. *Id.* (citing Ex. 1001, 18:14–15; Ex. 1003 ¶ 105). Petitioner concludes that “other animal anti-IL-11R α antibodies fall within the full scope of an ‘IL-11R α antibody’, including antibodies directed against other animal IL-11R and IL-11R α antigens.” *Id.* (citing Ex. 1003 ¶ 105).

Patent Owner does not propose a specific construction for the term “Interleukin 11 receptor α (IL-11R α) antibody” but disagrees with Petitioner’s construction to the extent it includes antibodies that bind to any species. Prelim. Resp. 17–19. According to Patent Owner, the “plain language of claim 1 requires administering the antibody ‘to [a] human subject in need of treatment’ in ‘a therapeutically effective amount’ for ‘treating fibrosis in [the] human subject.’” *Id.* at 18. Therefore, Patent Owner contends that Petitioner’s construction improperly fails to “giv[e] effect to all terms in the claim.” *Id.* at 17 (citing *Bicon v. Straumann*, 441 F.3d 945, 950 (Fed. Cir. 2006)).

We agree with Patent Owner that “Interleukin 11 receptor α (IL-11R α) antibody” should not be construed to include antibodies that bind to IL-11R α of non-human species but not to the human version of this protein because such a construction does not comport with the language of claim 1, which is clearly directed to treating a human subject. *See Pause Tech. v. TiVo*, 419 F.3d 1326, 1331 (Fed. Cir. 2005) (rejecting interpretation of claim element that ignored “other language appearing later in the claim” in stating that “[p]roper claim construction . . . demands interpretation of the entire claim in context, not a single element in isolation.”) (citing *Hockerson–Halberstadt, Inc. v. Converse Inc.*, 183 F.3d 1369, 1374 (Fed.Cir.1999)). Construing this term to include antibodies that bind solely to non-human IL-

11R α would be inconsistent with a claim directed to treatment of a human. Accordingly, for purposes of this decision, we construe “Interleukin 11 receptor α (IL-11R α) antibody” to mean “any natural or synthetic, monoclonal or polyclonal antibody made using any animal system including phage, or fragment or derivative thereof, that binds to human IL-11R α .”

Upon review of the parties’ arguments and the evidence of record, we determine that no other terms of the ’603 patent require express construction for purposes of this Decision. See *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (“[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.”)).

C. Asserted Lack of Written Description of Claims 1–10

Petitioner contends that claims 1–10 of the ’603 patent lack written description support. Pet. 22–27. Patent Owner disputes Petitioner’s contentions. Prelim. Resp. 20–44.

1. Principles of Law

To satisfy the written description requirement under 35 U.S.C. § 112(a), the specification must “reasonably convey[] to those skilled in the art that the inventor had possession” of the claimed invention as of the filing date. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). An adequate description does not require any particular form of disclosure or that the specification recite the claimed invention *in haec verba*, but must do more than render the claimed invention obvious. *Id.* at 1352. The written description requirement for a claimed genus requires the disclosure of “either a representative number of species falling

within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Id.* at 1350.

In evaluating the adequacy of the disclosure, a court may consider “the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.” *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005) (cited with approval in *Ariad*, 598 F.3d at 1352); *see also Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) (holding that because the assessment for written description is made from the perspective of a person of ordinary skill in the art, in some instances, a patentee can rely on information that is “well-known in the art” to satisfy written description).

2. *Petitioner’s Position*

Petitioner asserts that claims 1–10 of the ’603 patent lack written description support because “[n]o structural identification is provided for any species falling within the vast claimed genus of anti-IL-11R α antibodies.” Pet. 22 (citing Ex. 1003 ¶ 93). Petitioner argues that “there is no evidence within the ’603 patent ‘the ordinarily skilled artisan would be able to identify any compound based on its vague functional description’ . . . of binding to IL-11R α and inhibiting IL-11 mediated signaling by the anti-IL-11R α antibody.” *Id.* at 22–23 (quoting *Univ. of Rochester v. G.D. Searle Co.*, 358 F.3d 916, 928 (Fed. Cir. 2004)).

According to Petitioner, “[t]here is no guidance in the ’603 patent regarding the sequence/structural properties of the anti-IL-11R α antibodies that provide therapeutic benefit, their specificity, their binding affinity, or

binding epitope.” *Id.* at 24 (citing Ex. 1003 ¶ 116). Petitioner further asserts that “the ’603 patent provides no information that would allow [a person of ordinary skill in the art] to determine what antibody sequences would bind to an IL-11R α and be capable of inhibiting IL-11 mediated signaling in a human subject (*i.e.*, blocking the binding of IL-11 to an IL-11R or preventing signal transduction via the gp130 co-receptors).” *Id.* at 24–25 (citing Ex. 1003 ¶ 119). Petitioner also contends that the ’603 patent does not include any working examples of treating fibrosis with an IL-11R α antibody or of IL-11R α antibodies inhibiting IL-11 mediated signaling, and does not identify a structure/function correlation. *Id.* at 25–27 (citing Ex. 1003 ¶¶ 120–127, 130–135).

3. Patent Owner’s Position

Patent Owner argues that Petitioner’s written description arguments fail because, *inter alia*, they ignore the ’603 patent Specification’s disclosure of known antibodies suitable for use in the claimed method and ignore evidence establishing that a person of ordinary skill in the art was aware of numerous antibody species known to have the capabilities suitable for use in the claimed method of treatment. Prelim. Resp. 20–44.

4. Analysis

We agree with Patent Owner that Petitioner appears to have overlooked the ’603 patent Specification’s disclosure of anti-IL-11R α antibodies. Specifically, the ’603 patent lists “monoclonal antibody clone 025 (Sino Biological), clone EPR5446 (Abcam), clone 473143 (R & D Systems), clones 8E2 and 8E4 described in US 2014/0219919 A1 [Edwards] and the monoclonal antibodies described in Blanc et al (J. Immunol Methods. 2000 Jul. 31; 241(1–2); 43–59).” Ex. 1001, 18:41–46; Ex. 1003

¶ 176.⁶ Edwards, which Petitioner relies on for its obviousness and anticipation grounds, is directed to antibodies “that bind to IL-11R α and neutralize IL-11 signaling.” Ex. 1008 ¶ 13. Table 1 of Edwards lists clones 8E2 and 8E4 and sixty-three other antibodies (including variants of 8E2) as “exemplary IL-11R α -binding proteins.” *Id.* ¶ 362. Table 1 of Edwards also includes the sequence ID numbers for the heavy and light chains of the variable regions of each of these sixty-five clones and the amino acid sequences for each are disclosed in the sequence listing. *Id.* ¶ 362, p. 46–104.⁷

Furthermore, Table 3 of Edwards provides data regarding binding affinity (“K_D”) and potency (“as determined in BaF Human IL-11R cell proliferation assay”) for sixty-two variants of 8E2 identified in Table 1. *Id.* ¶ 492. The ’603 patent discloses that such “Ba/F3 cell proliferation assays” are suitable to assess whether an antibody can “[i]nhibit IL-11 mediated signaling.” Ex. 1001, 15:21–25, 17:41–44. The results in Table 3 of Edwards show that all but one or two⁸ of the sixty-two variants bind to IL-11

⁶ We note that Petitioner’s declarant, Dr. Bowers, references these examples of anti-IL-11R α antibodies provided in the ’603 patent Specification in stating that “[n]one of these clones claims to be functional, and therefore does not describe or bound a therapeutically active genus of antibodies.” Ex. 1003 ¶ 176. However, Petitioner fails to discuss this disclosure in the Petition other than broadly stating, in its enablement ground that, “[w]hile commercial antibodies are mentioned in the ’603 patent, their suitability is not suggested with regard to the putative anti-IL-11R α antibodies that allegedly have IL-11 binding activity.” Pet. 33.

⁷ The cited page numbers in Ex. 1001 refer to the page numbers in the original document at the top of the page.

⁸ No potency was shown for hu8E2-TS-13 and “an accurate K_D was difficult to determine” for hu8E2-TS-213. Ex. 1008 ¶ 492.

receptors “with a K_D of 1 μM or less” (i.e., 1×10^{-6}), consistent with the ’603 patent’s description of binding affinity for antibodies that can be used in the claimed method. Ex. 1001, 17:38–40; Ex. 1008 ¶ 492. Furthermore, sixty-one variants of 8E2 inhibited IL-11 mediated signaling, as demonstrated by “an IC_{50} of 10 $\mu\text{g/ml}$ or less,” also consistent with the ’603 patent’s description of inhibition for antibodies that can be used in the claimed method. Ex. 1001, 17:51–52; Ex. 1008 ¶ 492.

Petitioner’s failure to address the ’603 patent’s disclosure of known anti-IL-11R α antibodies results in their failure to consider “the specification as a whole” and the existing knowledge in the field, which renders their written description argument unpersuasive. *In re Wright*, 866 F.2d 422, 425 (Fed. Cir. 1989). We, therefore, determine that Petitioner has not presented sufficient persuasive evidence that the ’603 patent Specification fails to provide either a representative number of species or sufficient structural features to convey to a person of ordinary skill in the art that Patent Owner was in possession of the claimed invention. Accordingly, on this record, Petitioner has not established that it is more likely than not that the ’603 patent Specification lacks written description support for the claims.

D. Asserted Lack of Enablement of Claims 1–10

Petitioner contends that claims 1–10 of the ’603 patent are not enabled. Pet. 27–37. Patent Owner disputes Petitioner’s contentions. Prelim. Resp. 44–55.

1. Principles of Law

Under 35 U.S.C. § 112(a), enablement is separate and distinct from the written description requirement. *Ariad*, 598 F.3d at 1344. “The test of enablement is whether one reasonably skilled in the art could make or use

the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.” *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). “[A] patent specification complies with the statute even if a ‘reasonable’ amount of routine experimentation is required in order to practice a claimed invention.” *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999). Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors, referred to as the *Wands* factors, include:

(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id.

2. *Petitioner’s Position*

Petitioner asserts that “[t]he ’603 patent specification simply does not teach one of ordinary skilled [sic] in the art how to make and use the full scope of antibodies that inhibit IL-11 mediated signaling and treat fibrosis of the heart, liver, kidney, or eye as required by claims 1-10.” Pet. 28 (citing Ex. 1003 ¶ 28). Petitioner provides an analysis of the *Wands* factors (Pet. 28–37) and, similar to the written description arguments, asserts that “the sequences within the scope of the claims encompass a vast set of diverse antibodies” and “[t]here is no guidance in the ’603 patent regarding the sequence/structural properties of the claimed anti-IL-11R α antibodies.” Pet. 29 (citing Ex. 1003 ¶ 140, 141). Similarly, Petitioner argues:

neither the claims nor the '603 patent provides any guidance beyond the claimed functions for which antibody structures inhibit IL-11 mediated signaling and also treat fibrosis of the heart, liver, kidney, or eye if given in a therapeutically effective amount. [Ex. 1003 ¶ 144]. This requires one of ordinary skill in the art to design and screen an enormous number of antibodies to determine which bind to IL-11R α , and inhibit IL-11 mediated signaling, and treat fibrosis in at least one of the claimed organs, if administered to a human subject in a therapeutically effective amount. *Id.* As discussed above, the '603 patent fails to provide antibody structures or even epitope or information to identify or compare new antibodies with what is putatively disclosed in the patent.

Pet. 31.

3. Patent Owner's Position

Patent Owner contends that Petitioner's enablement argument fails for many of the same reasons as the written description ground including, *inter alia*, it is based on an improper claim construction, it "ignores the specification's disclosure of **known** antibodies suitable for use in the claimed method," and it "ignores the evidence establishing that a [person of ordinary skill in the art] was aware of numerous antibody species **known** to have capabilities suitable for use in the claimed method and could easily make more." Prelim. Resp. 44. With regard to claim construction, Patent Owner argues that Petitioner misstates the breadth of the claims (*Wands* Factor 8) because the Petition "depends on the extraordinary assertion that the specification fails to enable the claimed method of treating fibrosis in humans because it fails to enable the 'full scope of antibodies that inhibit IL-11 mediated signaling' for 'any species,' including antibodies that do **not** bind to **human** IL-11R α , and therefore **could not be used to practice the claimed invention.**" *Id.* at 45–46 (citing Pet. 28).

Furthermore, as with the written description ground, Patent Owner points out that Petitioner's enablement arguments ignore the '603 patent's disclosure of two antibody clones from Edwards and also ignores Edwards' teaching of sixty-two other anti-IL-11R α antibodies that are capable of binding to IL-11R α and neutralizing IL-11 signaling. Prelim. Resp. 47. (citing Ex. 1004 ¶ 78; Pet. 39). Patent Owner contends that a person of ordinary skill in the art would not have needed to design or screen a single antibody to practice claim 1, but could have used any of the numerous examples of anti-IL-11R α antibodies taught by Edwards. *Id.*

According to Patent Owner, the '603 patent "explains clearly that '[i]nhibition of IL-11 with a neutralizing antibody prevents TGF β 1-induced fibrosis.'" *Id.* at 48 (citing Ex. 1001, 7:48–49). Patent Owner also cites to Petitioner's declarant, Dr. Ledbetter who states that, "Edwards teaches anti-IL-11R α antibodies capable of binding to IL-11R α and neutralizing IL-11 signaling'" and that such antibodies "***can be successfully used to treat any condition*** that is caused by, or exacerbated by, IL-11 in a human subject.'" *Id.* at 48 (citing Ex. 1004 ¶ 78, ¶ 87 (alleging that inhibiting IL-11 signaling treats fibrosis)).

4. Analysis

We agree with Patent Owner that Petitioner misstates the breadth of the claims because they rely on an overly broad construction of the term "Interleukin 11 receptor α (IL-11R α) antibody" by including antibodies that bind only to non-human IL-11R α . As explained above, we construe this term to require binding to human IL-11R α .

We also agree with Patent Owner that Petitioner has again overlooked the '603 patent's disclosure of clones 8E2 and 8E4 from Edwards, which,

according to Petitioner's own declarant, are capable of being used in the claimed invention. See Ex. 1001, 18:41–46; Ex. 1004 ¶¶ 70, 72, 78, 87. As discussed above, Edwards provides the amino acid sequences for the heavy and light chain regions for sixty-five anti-IL-11R α antibodies, and discusses how to make these clones and obtain antibodies from phagemid libraries. Ex. 1008 ¶¶ 362, 482, 483, 489, 492, Table 1.

Petitioner's failure to adequately address the disclosure of these antibodies from Edwards pervades their analysis of the *Wands* factors and results in a failure to sufficiently establish that the claims of the '603 patent lack enablement. In view of the '603 patent's disclosure of anti-IL-11R α antibodies and Edwards' disclosure of how to obtain anti-IL-11R α antibodies, Petitioner has not established that undue experimentation would have been required to practice the claimed invention. Accordingly, on this record, Petitioner has not established that it is more likely than not that the claims of the '603 patent lack enablement.

E. Asserted Anticipation of Claims 1–4, 6, and 8–10 over Edwards (Ex. 1008)

Petitioner contends that the subject matter of claims 1–4, 6, and 8–10 of the '603 patent are inherently anticipated by the disclosure of Edwards as evidenced by Wynn or Chegini. Pet. 37–48. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 60–83.

1. Principles of Law

To establish anticipation under 35 U.S.C. § 102, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); *Karsten Mfg. Corp. v. Cleveland Golf Co.*,

242 F.3d 1376, 1383 (Fed. Cir. 2001). Each element of the challenged claim must be found, either expressly or inherently, in the single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). While the elements must be arranged or combined in the same way as in the claim, “the reference need not satisfy an *ipsissimis verbis* test,” i.e., identity of terminology is not required. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009); *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990). Thus, the dispositive question is whether one skilled in the art would have reasonably understood or inferred from a prior art reference that every claim element is disclosed in that reference. *Eli Lilly v. Los Angeles Biomedical Research Inst. at Harbor–UCLA Med. Ctr.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017).

2. *Edwards (Ex. 1008)*

As discussed *supra*, Edwards is directed to “proteins comprising antigen binding sites of antibodies that bind to interleukin-11 (IL-11) receptor alpha (IL-11R α) and uses thereof, e.g. in therapy.” Ex. 1008, code (57). Edwards teaches that IL-11 and/or IL-11R α is overexpressed in liver cancer, pancreatic cancer, gastric cancer, osteosarcoma, endometrial cancer and ovarian cancer. *Id.* ¶ 9. Edwards teaches that “IL-11 is also involved in other biological processes, such as, inhibition of adipogenesis, induction of cachexia (e.g., cancer cachexia), induction of febrile response, modulation of extracellular matrix metabolism, stimulation of acute-phase reactants and embryo implantation.” *Id.* ¶ 10.

Edwards describes the production of “[t]hree antibodies, 8E2, 8D10 and 8E4 [which] were isolated from a Fab-phagemid antibody library based on their ability to inhibit hIL-11 [human IL-11] dependent transfected BaF3

cell proliferation.” *Id.* ¶ 489. Edwards also describes the production of sixty-two additional binding site clones based on 8E2 and assesses their binding affinities and “relative ability to inhibit hIL-11 induced proliferation of BaF3 cells.” *Id.* ¶ 492.

Table 1 of Edwards lists clones 8E2, 8D10, 8E4, and the sixty-two variants of 8E2 as “exemplary IL-11R α -binding proteins” along with the sequence ID numbers for the amino acid sequences of the heavy and light chains of the variable regions of these clones. *Id.* ¶ 362, Table 1.

3. *Petitioner’s Position*

Petitioner asserts that Edwards teaches “anti-IL-11R α antibodies capable of binding to IL-11R α and neutralizing IL-11 signaling (*i.e.*, inhibiting IL-11 mediated signaling).” *Id.* at 39 (citing Ex. 1004 ¶ 78). Petitioner further contends that Edwards teaches administering a “therapeutically effective amount” of the antibodies to humans and, therefore, “discloses a method of treating a human subject, the method comprising administering to the human subject in need of treatment a therapeutically effective amount of an IL-11R α antibody.” *Id.* at 38–39 (citing Ex. 1004 ¶¶ 83, 88; Ex. 1008 ¶ 448).

Petitioner admits that Edwards fails to explicitly teach a method of treating fibrosis of the heart, liver, kidney, or eye, but asserts that Edwards inherently teaches a method of treating fibrosis of at least the heart and kidney. *Id.* at 39. According to Petitioner, Edwards teaches that anti-IL-11R α antibodies can be used to treat IL-11 mediated conditions, which are described in Edwards as being ““an autoimmune condition, an inflammatory condition, a wasting condition, bone conditions or cancer.”” *Id.* at 39–40 (citing Ex. 1008 ¶¶ 148, 159, 426; Ex. 1004 ¶¶ 73, 75, 77).

Petitioner further asserts that Edwards teaches treatment or prevention of “any condition that is caused by or exacerbated by IL-11” in a subject. *Id.* (citing Ex. 1004 ¶ 76; Ex. 1008 ¶ 426). According to Petitioner, such conditions “can include inflammatory conditions having fibrosis given that inflammation and fibrosis co-exist as pathologies in many liver, heart and kidney conditions” as exemplified by Box 1 of Wynn (shown below):

Box 1 | Important fibroproliferative diseases of humans

The United States government estimates that 45% of deaths in the United States can be attributed to fibrotic disorders. Fibrosis affects nearly all tissues and organ systems. Disorders in which fibrosis is a major cause of morbidity and mortality are listed.

Major-organ fibrosis

- Interstitial lung disease (ILD) — includes a wide range of distinct disorders in which pulmonary inflammation and fibrosis are the final common pathways of pathology. There are more than 150 causes of ILD, including sarcoidosis, silicosis, drug reactions, infections and collagen vascular diseases, such as rheumatoid arthritis and systemic sclerosis (also known as scleroderma). Idiopathic pulmonary fibrosis, which is by far the most common type of ILD, has no known cause.
- Liver cirrhosis — has similar causes to ILD, with viral hepatitis, schistosomiasis and chronic alcoholism being the main causes worldwide.
- Kidney disease — diabetes can damage and scar the kidneys, which leads to a progressive loss of function. Untreated hypertensive diseases can also contribute.
- Heart disease — scar tissue can impair the ability of the heart to pump.
- Diseases of the eye — macular degeneration and retinal and vitreal retinopathy can impair vision.

Fibroproliferative disorders

- Systemic and local scleroderma
- Keloids and hypertrophic scars
- Atherosclerosis and restenosis

Scarring associated with trauma (can be severe when persistent)

- Surgical complications — scar tissue can form between internal organs, causing contracture, pain and, in some cases, infertility
- Chemotherapeutic drug-induced fibrosis
- Radiation-induced fibrosis
- Accidental injury
- Burns

Id. at 40 (citing Ex. 1004 ¶ 78; Ex. 1010, 3⁹).

Furthermore, Petitioner asserts that one of the IL-11 mediated conditions exemplified in Edwards is “cachexia associated with or caused by cardiac disease or chronic kidney disease” and that, as taught in, for example, Wynn, “cardiac disease and chronic kidney disease are fibroproliferative diseases in humans.” *Id.* at 41 (citing Ex. 1004 ¶¶ 85, 88; Ex. 1008 ¶ 433; Ex. 1010, 3). According to Petitioner, “[b]ecause cardiac and chronic kidney diseases include fibrosis in those respective organs, any treatment of those diseases at least prevents further inducement of fibrosis in those organs or helps to alleviate some of the fibrosis in those organs.” *Id.* (citing Ex. 1004 ¶ 94). Petitioner further asserts that

[b]ecause of the nature and interrelatedness of cardiac disease and chronic kidney disease with fibrosis in those respective organs, Edwards necessarily benefits a human subject with fibrosis in the heart or kidney when treating cachexia associated with cardiac disease or chronic kidney disease with an anti-IL-11R α antibody that is capable of binding to IL-11R α and neutralizing IL-11 signaling.

Id. at 41–42 (citing Ex. 1004 ¶ 95). Petitioner concludes that “Edwards inherently teaches using anti-IL-11R α antibodies to treat fibrosis of the heart and kidney given at least the background reference of Wynn.”¹⁰ *Id.* at 42 (citing Ex. 1004 ¶ 95).

⁹ The cited page numbers in Ex. 1010 refer to the page numbers added by Petitioner in the bottom-right corner of the page.

¹⁰ We note that, although Petitioner states that “[c]laims 1–4, 6 and 8–10 are inherently anticipated by Edwards as evidenced by Wynn *or Chegini*” (Pet. 38) (emphasis added), Petitioner makes no specific arguments regarding Chegini in the anticipation section.

4. *Patent Owner's Position*

Patent Owner disputes Petitioner's characterization of Box 1 of Wynn and asserts that it refers to "inflammation" only once to describe "pulmonary inflammation" and never describes "inflammatory conditions . . . tied to the heart, liver, and kidney." Prelim. Resp. 56 (citing Pet. 39; Ex. 1010, 3).

Patent Owner also contends that "Petitioner fails to establish that the inflammatory condition mentioned in Edwards necessarily involves fibrosis" and points out that Wynn teaches that the mechanisms of inflammation and fibrosis are "distinct." *Id.* at 56–57 (citing Ex. 1010, Abstract).

Patent Owner further asserts that "***Edwards does not teach treating cardiac or kidney disease***; it only teaches treating cachexia, a separate condition that can be, but is not necessarily, caused by those diseases." *Id.* at 58. Furthermore, according to Patent Owner, Wynn does not teach that cachexia, nor cardiac or kidney disease causing cachexia, necessarily includes fibrosis. *Id.*

5. *Analysis*

We agree with Patent Owner that Petitioner has not established that Edwards inherently teaches treating a human who has fibrosis of the heart, liver, kidney, or eye. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Rapoport v. Dement*, 254 F.3d 1053, 1063 (Fed. Cir. 2001).

We agree that Wynn does not establish that treating an inflammatory condition necessarily treats fibrosis. In fact, Wynn teaches that

inflammation and fibrosis occur through “distinct” mechanisms. Ex. 1010, Abstract. Petitioner relies on Box 1 of Wynn to show that “[i]nflammatory conditions include many conditions tied to the heart, liver, and kidney;” however, “inflammation” only appears in Box 1 of Wynn in connection with Interstitial Lung Disease and not in connection with any heart, liver, or kidney disease. Pet. 40; Ex. 1010, 3. Therefore, Petitioner has not established that Edwards’ treatment for inflammation would inherently (i.e., necessarily) treat fibrosis of the heart, liver or kidney.

We also agree with Patent Owner that Petitioner fails to establish that Edwards’ disclosure of treating cachexia associated with or caused by cardiac disease or chronic kidney disease necessarily treats fibrosis. First, Edwards does not actually teach treating heart or kidney disease but, rather, teaches the treatment of cachexia, a “wasting condition . . . associated with or caused by” many different diseases. Ex. 1008 ¶ 433. Petitioner has not established that treating cachexia arising from a potential cardiac or kidney disease would necessarily treat fibrosis, which may or may not be present. *See Perricone v. Medicis Pharm*, 432 F.3d 1368, 1379 (Fed. Cir. 2005) (finding no inherent anticipation of claimed new use of known composition to treat sunburn where prior art only taught applying the composition to skin, because while skin may be sunburned it is not necessarily so). Furthermore, while Wynn Box 1 mentions forms of cardiac and kidney disease that involve scarring, it does not state that all cardiac and chronic kidney disease involves scarring or fibrosis. Ex. 1010, 3.

In view of the above, on this record, Petitioner has failed to show that Edwards in view of Wynn inherently anticipates the claims of the ’603 patent. Accordingly, Petitioner has not shown that it is more likely than not

that the claims of the '603 patent are unpatentable for anticipation over Edwards.

F. Asserted Obviousness of Claims 1–10 over Edwards (Ex. 1008)

Petitioner contends that the subject matter of claims 1–10 of the '603 patent are obvious over the disclosure of Edwards. Pet. 48–54. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 69–83.

1. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the subject matter sought to be patented and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) when in evidence, objective evidence of non-obviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A patent claim “is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. An obviousness determination requires finding “both ‘that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.’” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016) (citation omitted); *see KSR*, 550 U.S. at 418 (for an

obviousness analysis, “it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does”). Furthermore, an assertion of obviousness “cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR*, 550 U.S. at 418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)); see *In re Nuvasive, Inc.*, 842 F.3d 1376, 1383 (Fed. Cir. 2016) (a finding of a motivation to combine “must be supported by a ‘reasoned explanation’” (citation omitted)).

2. *Petitioner’s Position*

Petitioner asserts that “[t]o the extent the Board finds that Edwards does not inherently teach treating fibrosis in the heart, liver, kidney, or eye, it would have been obvious to one of ordinary skill in the art to extend the treatment described in Edwards to treat fibrosis in organs, such as heart, liver, kidney, and eye.” Pet. 49. Specifically, Petitioner, with supporting testimony from Dr. Ledbetter, contends that a person of ordinary skill in the art would have understood that tissue fibrosis “is always accompanied with a robust, profibrogenic TH2 immune response, which is described in the review article by Wynn for example in Box 1 and on page 584 (Ex. 1010).” *Id.* (citing Ex. 1004 ¶ 87). According to Petitioner and Dr. Ledbetter:

The understanding of the role of Th2 cytokines (IL-13 and IL-4 in particular) was well documented already by December 2015 for stimulating the release of potent profibrogenic cytokines, of which the most prominent are TGFβ and IL-11. [Ex. 1004 ¶ 87]. It has been known since about 2005 that IL-11 is strongly stimulated by TGFβ. In particular, IL-11 has been associated with pulmonary fibrosis in experimental models and

in humans since at least 1996. *Id.* (citing Exs. 1068, 1069). To a person of ordinary skill in the art, it would be scientifically reasonable and expected that therapeutic neutralization of IL-11 signaling would ameliorate pathogenic tissue fibrosis already by December 2015. *Id.*

Id. at 49–50.

Based on these contentions, Petitioner asserts that Edwards’ disclosure of a method for treating or preventing an IL-11 mediated condition by administering an IL-11-R α antibody renders the treatment of tissue fibrosis obvious. *Id.* at 50 (citing Ex. 1004 ¶ 88). Petitioner also asserts that Edwards’ disclosure of the treatment or prevention of any condition that is caused or exacerbated by IL-11 can include “inflammatory conditions having fibrosis given that inflammation and fibrosis co-exist as pathologies in many liver, heart, and kidney conditions.” *Id.* (citing Ex. 1004 ¶ 78).

Similar to the anticipation arguments, Petitioner also contends that “based on the knowledge of one [of] ordinary skill as evidenced by Wynn, it would have been obvious to one of ordinary skill in the art that there is a clinical relationship between fibrosis and cardiac disease or chronic kidney disease.” *Id.* at 51 (citing Ex. 1004 ¶ 96). According to Petitioner, based on this relationship, it would have been obvious to a person of ordinary skill in the art “to extend the treatment of cardiac disease and chronic kidney disease in Edwards to treatment of fibrosis in the heart and kidney” and they would have had a reasonable expectation of success because Edwards “teaches that anti-IL-11R α antibodies can be used to treat cachexia associated with or caused by fibrosis in the heart or in chronic kidney disease.” *Id.* at 51–52 (citing Ex. 1004 ¶¶ 96, 122).

Petitioner further asserts that “Edwards teaches that it was known in the art that neutralizing IL-11 signaling can be used to treat a Th2-mediated disorder, such as asthma.” *Id.* at 50 (citing Ex. 1004 ¶ 81). According to Petitioner, asthma induces fibrosis in the lamina reticularis; therefore, “treatment of asthma at least prevents further inducement of fibrosis in the lamina reticularis.” *Id.* at 51 (citing Ex. 1004 ¶ 81; Ex. 1005, 1:46).

Lastly, Petitioner asserts that “if the ’603 patent is found to be enabled for the full scope of claim 1, treating fibrosis of any organ should have been obvious based on the finding that it was known or obvious to treat fibrosis in any other organ.” *Id.* at 52. This argument is based on Petitioner’s assertion that the ’603 patent only provides data related to *in vitro* studies related to cardiac cells and provides only prophetic examples to extend treatment to organs other than the heart such as the kidney, liver, and eye. *Id.* (citing Ex. 1004 ¶ 86). Petitioner concludes that “because Edwards teaches treatment of asthma, one form of fibrosis in the lungs, cardiac disease, or chronic kidney disease, it would have been obvious to extend the treatment described in Edwards to fibrosis in other organs, such as heart, liver, kidney, and eye.” *Id.* at 53 (citing Ex. 1004 ¶ 93).

3. Patent Owner’s Position

Patent Owner asserts that Petitioner’s obviousness arguments fail for the same reasons as the anticipation ground and also fail because Petitioner ignored references discussed in the ’603 patent, which taught that IL-11 was protective against cardiac, liver, and kidney fibrosis. Prelim. Resp. 71–73 (citing Ex. 2003; Ex. 2005; Ex. 2006; Ex. 2007). Patent Owner argues that these references taught away from treating fibrosis by administering antibodies that would inhibit IL-11 mediated signaling. *Id.*

Patent Owner also contends that Petitioner fails to establish that IL-11 was believed to cause fibrosis of any claimed organ; therefore, a person of ordinary skill in the art would not have been motivated to inhibit IL-11 to treat fibrosis (especially in view of the art's teachings that elevated IL-11 could be a protective response). *Id.* at 75. Patent Owner further asserts that Petitioner does not explain the alleged “clinical relationship” between fibrosis and cardiac/kidney disease or why such relationship would have caused a person of ordinary skill in the art to “extend the treatment of cachexia associated with cardiac disease or chronic kidney disease to cardiac or kidney fibrosis.” *Id.* at 79 (citing Pet. 51).

In response to Petitioner's argument that Edwards' disclosure of treating asthma renders obvious treating fibrosis of any organ, Patent Owner contends that the assertion that “asthma induces fibrosis” is unsupported. *Id.* at 80. Also, according to Patent Owner, Petitioner's arguments regarding the experimental data in the '603 patent are irrelevant and incorrect (citing examples in the '603 patent directed to data for various types of tissues and cells). *Id.* at 80–82 (citing Ex. 1001 45:25–42, 45:43–46:2, 48:12–49:41, Figures 21B–21C, 27–29, 38A–38D, 39).

Lastly, Patent Owner asserts that Petitioner's obviousness theories are refuted by objective evidence of nonobviousness such as the contemporaneous praise in “highly prestigious technical journals noting the ‘surprising’ results discovered by the inventors.” *Id.* at 83 (citing Ex. 2002; Ex. 1066). According to Patent Owner, such evidence “directly refutes the Petition's hindsight assertion that it was known that IL-11 caused fibrosis and ‘obvious’ to treat fibrosis by inhibiting IL-11.” *Id.*

4. *Analysis*

We agree with Patent Owner that Petitioner has not shown that it would have been obvious to one of ordinary skill in the art that inhibiting IL-11 mediated signaling would be effective in treating fibrosis of the heart, liver, kidney, or eye. First, in making their obviousness arguments, Petitioner fails to address the prior art cited in the '603 patent which taught that IL-11 was beneficial in preventing fibrosis. For example, Obana¹¹ (cited in Ex. 1001, 2:2–10), taught that IL-11 was protective against cardiac fibrosis and stated that “[t]hese findings suggest that IL-11 treatment is a promising strategy.” Ex. 2003, 684, 689¹² (“Activation of the IL-11/glycoprotein 130/STAT3 axis may be a novel therapeutic strategy against cardiovascular diseases.”). Furthermore, Ham¹³ (cited in Ex. 1001, 2:14–18), taught that IL-11 is protective of a form of kidney disease and stated that “prolonged and high-dose IL-11 therapy does not induce tissue fibrosis.” Ex. 2006, 1398.¹⁴ In addition, Zhu¹⁵ (cited in Ex. 1001, 2:20–25), taught that IL-11 protects the liver against reperfusion injury and stated that,

¹¹ Obana, Masanori, et al., Therapeutic Activation of Signal Transducer and Activator of Transcription 3 by Interleukin-11 Ameliorates Cardiac Fibrosis after Myocardial Infarction, *Circulation* 121, 684–691 (2010) (“Obana”).

¹² The cited page numbers in Ex. 2003 refer to the page numbers in the original document at the bottom of the page.

¹³ Ham, Ahrom, et al., Critical Role of Interleukin-11 in Isoflurane-mediated Protection against Ischemic Acute Kidney Injury in Mice, *Anesthesiology* 119, 1389–1401 (2013) (“Ham”).

¹⁴ The cited page numbers in Ex. 2006 refer to the page numbers in the original document at the bottom of the page.

¹⁵ Zhu, Miao, et al., IL-11 Attenuates Liver Ischemia/Reperfusion Injury (IRI) through STAT3 Signaling Pathway in Mice, *PLoS One* 10(5), 1–15 (2015) (“Zhu”).

“[i]n cardiac myocytes, IL-11 treatment attenuates injury and fibrosis.” Ex. 2007, 12.¹⁶ See also Ex. 2005 (teaching that IL-11 suppresses extracellular matrix deposition, which is necessary for fibrosis (see Ex. 1001, 33:26–44)). Petitioner and Dr. Ledbetter do not adequately explain why a person of ordinary skill in the art would have found it obvious to treat cardiac, kidney, liver, or eye fibrosis with an IL-11R α binding antibody capable of inhibiting IL-11 mediated signaling in light of the art cited above. “[I]n an obviousness analysis, prior art should be viewed as a whole,” including references that taught away from the claimed invention. *Impax Labs. v. Lannett Holdings*, 893 F.3d 1372, 1379–1381 (Fed. Cir. 2018).

Similarly, Petitioner’s argument regarding the accompaniment of fibrosis with TH2 cytokines fails to consider the prior art as a whole. In alleging that, as of December 2015, it would have been expected that neutralization of IL-11 signaling would ameliorate fibrosis, Petitioner cites to paragraph 87 of the Ledbetter Declaration. Pet. 50. Paragraph 87 of the Ledbetter Declaration cites to Minshall¹⁷ as evidence that overexpression of IL-11 within the lungs results in fibrosis. Ex. 1004 ¶ 87. However, Dr. Ledbetter fails to acknowledge the portion of Minshall which states that

[t]he mechanisms whereby IL-11 exerts its activity in the airways are complex. IL-11 has previously been shown to have fibrogenic potential in an animal model . . . However, in our in vivo study we have not been able to show any correlation between IL-11 expression in bronchial biopsy specimens and

¹⁶ The cited page numbers in Ex. 2007 refer to the page numbers in the original document at the bottom of the page.

¹⁷ Minshall, Eleanor, et al., IL-11 expression is increased in severe asthma: Association with epithelial cells and eosinophils, *J. Allergy Clin. Immunol.* 105, 232–238) (2000) (“Minshall”).

types I or III collagens, although tissue fibrosis correlates with the disease severity . . . To date, there is a scarcity of literature documenting the mechanisms responsible for the fibrotic response.

Ex. 1069, 236–237.¹⁸ Minshall also states that “[w]hether IL-11 exerts predominantly proinflammatory or anti-inflammatory actions within the airways remains to be elucidated.” *Id.* at 237. Petitioner fails to sufficiently show how such a disclosure would have rendered it obvious to a person of ordinary skill in the art to use IL-11R α antibodies to treat fibrosis of the heart, liver, kidney, or eye.

Petitioner’s arguments with respect to Wynn also do not sufficiently show that the challenged claims would have been obvious. As discussed *supra*, Wynn does not teach that inflammatory conditions are tied to the heart, liver or kidney and, in fact, teaches that inflammation and fibrosis occur through “distinct” mechanisms. Ex. 1010, Abstract. With respect to Petitioner’s argument that Edwards teaches that anti-IL-11R α antibodies can be used to treat cachexia associated with or caused by fibrosis in the heart or kidney (Pet. 52), as discussed *supra*, Edwards does not teach treatment of cardiac or kidney disease and neither Petitioner nor Dr. Ledbetter sufficiently explain the relationship between fibrosis and cardiac or kidney disease such that a person of ordinary skill in the art would have been motivated to use anti-IL-11R α antibodies to treat fibrosis in the heart or kidney with a reasonable expectation of success.

¹⁸ The cited page numbers in Ex. 1069 refer to the page numbers in the original document at the top-left and right side of the page.

Petitioner's arguments regarding Edwards' disclosure of the treatment of asthma also fails. Petitioner fails to show that asthma was known to induce fibrosis nor do they sufficiently show why Edwards' disclosure of treatment of a different organ (the lungs) for a different disease (asthma), would render obvious treatment of fibrosis in the heart, liver, kidney, or eye, especially in light of the teachings of Exhibits 2003, 2005, 2006, and 2007 discussed *supra*.

In view of the foregoing, as we balance Petitioner's arguments and evidence that the claims of the '603 patent are unpatentable as having been obvious over Edwards, we conclude that the evidence weighs against a conclusion of obviousness.

a. Objective Indicia of Nonobviousness

In determining whether a claim is obvious in light of the prior art, we also consider any relevant evidence of secondary considerations of non-obviousness. *See Graham*, 383 U.S. at 17. Notwithstanding what the teachings of the prior art would have suggested to one of ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of non-obviousness, may lead to a conclusion that the challenged claims would not have been obvious to one of ordinary skill. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Patent Owner presents evidence of industry praise. Prelim. Resp. 83.

“In order to accord substantial weight to secondary considerations in an obviousness analysis, the evidence of secondary considerations must have a nexus to the claims, i.e., there must be a legally and factually sufficient connection between the evidence and the patented invention.” *Fox Factory*,

Inc. v. SRAM, LLC, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (internal quotations omitted).

Evidence that the industry praised a claimed invention or a product that embodies the patent claims weighs against an assertion that the same claim would have been obvious. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1334 (Fed. Cir. 2016). As evidence of industry praise, Patent Owner asserts that “[t]he inventors’ ground-breaking work was contemporaneously recognized” and cite to the publication of the claimed method for treating fibrosis in the “prestigious peer-reviewed journal *Nature*.” Prelim. Resp. 2 (citing Ex. 1066). Patent Owner also cites to a later journal article by King¹⁹ which selected the *Nature* article as an “editor’s choice” and “praise[d] the inventors for having ‘discovered a **surprising** role for interleukin-11 (IL-11)’ in treating fibrosis.” *Id.* (citing Ex. 2002).

The *Nature* article cited by Patent Owner describes the discovery that “upregulation of interleukin-11 (IL-11) is the dominant transcriptional response to TGFβ1 exposure and required for its pro-fibrotic effect.” Ex. 1066, 1.²⁰ The article discusses how IL-11 injection caused heart and kidney fibrosis and discusses the use of an anti-IL-11Rα antibody. *Id.* at 1, 2, 7. The article concludes:

Therefore, inhibition of IL-11 prevents fibroblast activation across organs and species in response to a range of important pro-fibrotic stimuli. These results reveal a central role of IL-11

¹⁹ Kevin King, A scar-y movie, starring IL-11, *Science Translational Medicine*, Vol. 9, 418 (2019) (“King”). We note that the version of this article submitted as Exhibit 2002 appears to be missing some pages.

²⁰ The cited page numbers in Ex. 1066 refer to the page numbers added by Petitioner in the bottom-right corner of the page.

in fibrosis and we propose that inhibition of IL-11 is a potential therapeutic strategy to treat fibrotic diseases.

Id. at 1. The King article, published in *Science Translational Medicine*, refers to the *Nature* article, which it credits for the discovery of “a surprising role for interleukin-11 (IL-11)” and states, “[s]urprisingly, stimulation of fibroblasts with IL-11 increased ECM production without altering gene expression.” Ex. 2002, 1–2.²¹

Because the articles describe experiments related to fibrosis of the heart and kidney and refer to the use of an anti-IL-11R α antibody, we determine that this evidence is probative in establishing that the asserted objective evidence is tied to use of an IL-11R α antibody to treat fibrosis of the heart or kidney, as disclosed in the '603 patent claims.²²

“The objective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis.” *WBIP*, 829 F.3d at 1328. Indeed, the Federal Circuit has held that such evidence “may often be the most probative and cogent evidence in the record.” *Id.* (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)). Overall, we determine that Patent Owner’s evidence of industry praise weighs in favor of nonobviousness.

Factual inquiries for an obviousness determination include secondary considerations based on objective evidence of nonobviousness. *Graham v.*

²¹ The cited page numbers in Ex. 2002 refer to the page numbers added by Patent Owner in the bottom-right corner of the page.

²² We note that there may be less of a nexus to the limitations of the claims directed to treatment of fibrosis in the liver or eye; however, Petitioner has not provided persuasive evidence to show that these limitations would have been obvious.

John Deere Co., 383 U.S. 1, 17–18 (1966). We conclude that, on this record, Petitioner has not shown that claims 1–10 would have been obvious over the teachings of Edwards because we determine that Petitioner’s arguments do not sufficiently establish obviousness and the objective indicia of nonobviousness also weigh in favor of nonobviousness. Based on the disclosure in the ’603 patent Specification and the similar disclosure in the articles cited by Patent Owner, we conclude there is a nexus between the industry praise and the challenged claims. Accordingly, on this record, Petitioner has not shown that it is more likely than not that the claims of the ’603 patent are unpatentable for obviousness over Edwards.

G. Asserted Obviousness of Claims 1–10 over Edwards (Ex. 1008), Wynn (Ex. 1010), and Chegini (Ex. 1065)

Petitioner contends that the subject matter of claims 1–10 of the ’603 patent are obvious over the disclosure of Edwards, Wynn, and Chegini. Pet. 54–62. Patent Owner disputes Petitioner’s contentions. Prelim. Resp. 83–89.

1. Wynn (Ex. 1010)

Wynn discusses the molecular mechanisms of wound healing and fibrosis. Ex. 1010, Abstract. Wynn states that current treatments for fibrotic disorders “target the inflammatory cascade, but they have been widely unsuccessful, largely because the mechanisms that are involved in fibrogenesis are now known to be distinct from those involved in inflammation.” *Id.* Box 1 of Wynn provides a list of important fibroproliferative diseases in humans. *Id.* at 585.

2. *Chegini (Ex. 1065)*

Chegini teaches “a method for detecting a fibrotic disorder in a subject by . . . analyzing the expression of at least one gene that is differentially expressed in the fibrotic disorder of interest . . .” Ex. 1065

¶ 13. Chegini discusses preferentially treating a fibrotic disorder of the female reproductive tract. *Id.* Specifically, Chegini states:

Based on previous and present observations, the present inventors propose that a local inflammatory response mediated through individual and combined actions of TGF- β , IL-13 and IL-11, as well as regulatory function of TGF- β on EGR expression, results on local expression of set of genes whose products promote apoptotic and non-apoptotic cell death, further enhancing an inflammatory reaction that orchestrate various events leading to progression of fibrosis in leiomyoma.

Id. ¶ 200.

3. *Petitioner’s Position*

Petitioner argues that it would have been obvious to a person of ordinary skill in the art “to extend the treatment described in Edwards to treat fibrosis in the heart, liver, kidney, and eye, in view of Wynn and Chegini.” Pet. 54. Petitioner asserts that it was known in the art that elevated expression of IL-11 is indicative of a fibrotic disorder as evidenced by Chegini. *Id.* (citing Ex. 1004 ¶ 97). Petitioner also contends that Chegini “associates a local inflammatory response to be mediated through TGF- β , IL-13 and IL-11, which enhances the inflammatory reaction.” Pet. 55 (citing Ex. 1065 ¶ 200; Ex. 1004 ¶ 97).

According to Petitioner, Chegini discloses that its invention is useful for treating fibrosis, which includes “pathophysiological conditions such as renal failure, liver cirrhosis and heart disease.” *Id.* (citing Ex. 1065 ¶ 13; Ex. 1004 ¶ 98). Petitioner asserts that, based on this teaching, a person of

ordinary skill in the art “would have therefore understood that blocking IL-11 mediated signaling would provide a benefit to a human subject suffering from fibrosis in the heart, liver or kidney.” *Id.* at 54–55 (citing Ex. 1004 ¶ 100). Petitioner also contends that “[b]ased on the teachings of Edwards, it would have been obvious to block IL-11 mediated signaling by using an anti-IL-11R α antibody that inhibits IL-11 signaling as disclosed in Edwards.” *Id.* at 56 (citing Ex. 1004 ¶ 100). Petitioner concludes, “[a]ccordingly, it would have been obvious based on the teachings of Edwards and Chegini to treat fibrosis of the heart, liver or kidney by administering a therapeutically effective amount of an anti-IL-11R α antibody disclosed in Edwards. *Id.* (citing Ex. 1004 ¶ 100).

4. *Patent Owner’s Position*

In addition to reiterating arguments made in response to Petitioner’s other anticipation and obviousness grounds, Patent Owner also asserts that Chegini does not teach that fibrosis of the claimed organs is caused by IL-11. Prelim. Resp. 84–87. Patent Owner references paragraph 200 of Chegini, cited by Petitioner, and points out that this paragraph refers to fibrosis in leiomyoma, which is a uterine tumor. *Id.* at 84–85 (citing Ex. 1065 ¶¶ 4, 13, 200). Therefore, according to Patent Owner, the fibrosis discussed in Chegini is fibrosis in the uterus, not of the claimed organs. *Id.* at 85.

5. *Analysis*

As discussed *supra*, Petitioner has not presented sufficient evidence to show that Edwards, with the knowledge of one of ordinary skill in the art as evidenced by Wynn, renders the claims of the ’603 patent obvious. We do not find that Chegini cures the deficiencies of these two references. While

Chegini broadly discloses that elevated expression of IL-11 “is indicative of a fibrotic disorder,” it specifically teaches that IL-11 may be involved in “an inflammatory reaction” that “leads to the progression of fibrosis in leiomyoma,” which is a uterine tumor. Ex. 1065 ¶¶ 4, 13, 16, 200. Furthermore, Wynn states that “the mechanisms that are involved in fibrogenesis are now known to be distinct from those involved in inflammation.” Ex. 1010, Abstract. Petitioner and Dr. Ledbetter do not adequately explain why Chegini’s disclosure of a potential relationship between IL-11 and fibrosis in a uterine tumor would have motivated a person of ordinary skill in the art to use anti-IL-11R α antibodies to treat fibrosis in the heart, kidney, liver, or eye with a reasonable expectation of success.

Furthermore, while Petitioner cites to the disclosure in Chegini which states that “[f]ibrosis is involved in . . . pathophysiological conditions such as renal failure, liver cirrhosis and heart disease” (Ex. 1065 ¶ 13), Petitioner fails to acknowledge or discuss the prior art discussed *supra* which taught that IL-11 was expected to prevent fibrosis in heart, kidney, and liver cells. See Ex. 2003, 2005, 2006, and 2007. See *Medichem v. Rolabo*, 437 F.3d 1157, 1165–66 (Fed. Cir. 2006) (“Where the prior art contains ‘apparently conflicting’ teachings... each reference must be considered. . . .”; “[T]he prior art must be considered as a whole for what it teaches.”).

In light of this omission, Petitioner and Dr. Ledbetter fail to adequately explain why a person of ordinary skill in the art would have been motivated to, or would have had a reasonable expectation of success, in treating fibrosis of the heart, liver, kidney, or eye by administering an anti-IL-11R α antibody. Furthermore, as discussed *supra*, Patent Owner has

presented evidence of objective indicia of nonobviousness which weighs in favor of non-obviousness.

Accordingly, on this record, Petitioner has not shown that it is more likely than not that the claims of the '603 patent would have been obvious over the combined disclosures of Edwards, Wynn, and Chegini.

H. 35 U.S.C. § 325(d)

Patent Owner contends we should exercise our discretion under 35 U.S.C. § 325(d) to deny the Petition because the “Petition’s § 112 grounds directly challenge [the Examiner’s] finding that ‘the claimed invention meets the requirements of . . . 35 U.S.C. § 112’” and because Edwards is incorporated by reference in the '603 patent and cited on the face of the patent. Prelim. Resp. 89–90. Because we have considered the merits of the Petition and decline to institute a post-grant review on that basis, Patent Owner’s arguments with respect to 35 U.S.C. § 325(d) are moot.

III. CONCLUSION

For the reasons set forth above, we determine Petitioner fails to demonstrate it is more likely than not that any of claims 1–10 of the '603 patent are unpatentable on the grounds asserted in the Petition. Thus, we do not institute a post-grant review with respect to the challenged claims.

ORDER

It is

ORDERED that the Petition is *denied* and no post-grant review is instituted.

PGR2019-00053
Patent 10,106,603 B2

PETITIONER:

Christopher Bruenjes
christopher.bruenjes@dbr.com

Mercedes Meyer
mercedes.meyer@dbr.com

William Foster
william.foster@dbr.com

PATENT OWNER:

Edward R. Gates,
EGates-PTAB@wolfgreenfield.com

Elisabeth H. Hunt
EHunt-PTAB@wolfgreenfield.com

Richard F. Giunta
RGiunta-PTAB@wolfgreenfield.com