

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GLAXOSMITHKLINE LLC,
Petitioner,

v.

FIBROGEN, INC.,
Patent Owner.

Case IPR2016-01315
Patent 8,466,172 B2

Before TONI R. SCHEINER, SHERIDAN K. SNEDDEN, and
SUSAN L. C. MITCHELL, *Administrative Patent Judges*.

MITCHELL, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

A. Background

Petitioner GlaxoSmithKline LLC (“Petitioner”) filed a Petition (Paper 2, “Pet.”) requesting an *inter partes* review of claims 1–8 (the “challenged claims”) of U.S. Patent No. 8,466,172 B2 (Exhibit 1001, “the ’172 patent”). See 35 U.S.C. §§ 311–319. Patent Owner FibroGen, Inc. (“Patent Owner”) filed a Preliminary Response. Paper 9 (“Prelim. Resp.”).

We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314 and 37 C.F.R. § 42.4(a). To institute an *inter partes* review, we must determine that the information presented in the Petition shows “a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). For the reasons set forth below, we conclude that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one of the challenged claims of the ’172 patent. Therefore, we deny institution of an *inter partes* review for claims 1–8 of the ’172 patent.

B. Related Proceedings

Both parties indicate that the ’174 patent is not involved in any co-pending litigation or administrative matters, but Petitioner filed the following five additional requests for *inter partes* review of other patents owned by FibroGen: IPR2016-01318 (involving U.S. Patent No. 8,609,646); IPR2016-01319 (involving U.S. Patent No. 8,614,204); IPR2016-01320 (involving U.S. Patent No. 8,604,013); IPR2016-01322 (involving U.S. Patent No. 8,604,012); and IPR2016-01323 (involving U.S. Patent No. 8,629,131). Pet. 50; Paper 7, 1.

C. The '172 Patent (Ex. 1001)

The '172 patent involves methods of stabilizing the alpha subunit of hypoxia inducible factor (“HIF”) to prevent, pretreat, or treat conditions associated with HIF including ischemic and hypoxic conditions. Ex. 1001, Abst. Such methods specifically involve inhibiting hydroxylation of HIF α by inhibiting HIF prolyl hydroxylase enzyme activity, (*id.* at 3:62–4:12), and in one particular method involve inhibiting hydroxylation of at least one amino acid residue in HIF α (*id.* at 4:52–55).

The term “hypoxia” is expressly defined as referring “to an environment with levels of oxygen below normal,” (*id.* at 21:44–45), and the term “ischemia” is expressly defined as referring “to a reduction in blood flow” (*id.* at 21:18). It is also stated in the '172 patent that

[i]schemia may arise due to conditions such as atherosclerosis, formation of a thrombus in an artery or vein, or blockage of an artery or vein by an embolus, vascular closure due to other causes, e.g., vascular spasm, etc. Such conditions may reduce blood flow, producing a state of hypoperfusion to an organ or tissue, or block blood flow completely.

Id. 21:19–26.

D. Illustrative Claims

Of the challenged claims, claim 1 is the sole independent claim of the '172 patent. The remaining challenged claims 2–8 depend directly or indirectly from claim 1. Claim 1 is illustrative of the challenged claims and recites:

1. A method for treating a hypoxic or ischemic disorder or condition in a subject, the method comprising administering to the subject an effective amount of heterocyclic

carboxamide compound that stabilizes the alpha subunit of hypoxia inducible factor (HIF α).

Ex. 1001, 63:32–36.

E. The Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable based on the following grounds. Pet. 4.

References	Basis	Claims Challenged
Weidmann ¹	§ 102(b)	1–3, 5, 6, and 8
Ivan ² and Bickel ³	§ 103(a)	1–3, 5, and 6
Ivan, Bickel, and Weidmann	§ 103(a)	8
Ivan, Bickel, and Semenza ⁴	§ 103(a)	4 and 7

Petitioner relies also on the Declaration of Paul T. Schumacker, Ph.D. Pet. 1–49; *see* Ex. 1002 (Schumacker Decl.).

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest

¹ U.S. Patent No. 6,093,730, issued July 25, 2000 (Ex. 1019, “Weidmann”).

² Mircea Ivan et al., *HIF α Targeted for VHL-Mediated Destruction by Proline Hydroxylation: Implications for O₂ Sensing*, 292 Science 542–46 (2001) (Ex. 1025, “Ivan”).

³ Martin Bickel et al., *Selective Inhibition of Hepatic Collagen Accumulation in Experimental Liver Fibrosis in Rats by a New Prolyl 4-Hydroxylase Inhibitor*, 28 Hepatology 404–11 (1998) (Ex. 1027, “Bickel”).

⁴ Gregg L. Semenza, *HIF-1 and Human Disease: One Highly Involved Factor*, 14 Genes & Dev. 1983–991 (2000) (Ex. 1009, “Semenza”).

reasonable interpretation approach, claim terms are given their ordinary and customary meaning as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

1. “*Heterocyclic Carboxamide Compound*”

Petitioner offers an interpretation of the claim term “heterocyclic carboxamide compound” as “any compound that contains a heterocyclic ring and a carboxamide moiety. A carboxamide moiety has the general formula R-CO-NR’R” wherein R, R’ and R” are organic substituents or hydrogen.” Pet. 13 (citing Ex. 1002 ¶ 31). Although Patent Owner points out that Petitioner provides no intrinsic support for this interpretation, it does not offer an interpretation of its own. Prelim. Resp. 7–8.

Because the parties do not appear to disagree about whether the art teaches such compounds, *see* Pet. 20–23; Prelim. Resp. 2, 25, 27–28 (asserting conditions and dosages of compounds used in the ’172 patent and Weidmann are different, not that the compounds themselves are distinct), and our decision does not require an express construction to resolve the dispute, we do not need to interpret expressly the claim term “heterocyclic carboxamide compound.” *See, e.g., Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

2. “*The Subject*”

Patent Owner offers interpretations of the claim term “the subject” recited in claim 1 and the preamble of claim 1, “[a] method for treating a

hypoxic or ischemic disorder or condition.” Prelim. Resp. 8–11. Petitioner offers no express construction for these claim terms. *See* Pet. 13.

Patent Owner states that “subject” in the body of claim 1 refers back to the subject delineated in the preamble as one having “a hypoxic or ischemic disorder or condition,” providing antecedent basis for “the subject.” Prelim. Resp. 8. Thus, Patent Owner concludes that “the subject” should be interpreted as “a subject having a hypoxic or ischemic disorder or condition.” *Id.*

We note that the ’172 patent expressly defines the term “subject,” stating it is to be used in its “broadest sense,” Ex. 1001, 24:35, and does not so limit the scope of the term “subject” itself. Specifically, the ’172 patent sets forth that “subject” may include “isolated cells, either prokaryotic or eukaryotic, or tissues grown in culture. Preferably, subjects include animals, particularly a mammalian species including rat, rabbit, bovine, ovine, porcine, murine, equine, and primate, particularly human.” *Id.* at 24:36–40.

Thus, the question becomes whether, in the context of the claims, the preamble reciting a method for treating “a hypoxic or ischemic disorder or condition *in a subject*” is limiting. Patent Owner asserts that it is. *See* Prelim. Resp. 8–10; *see id.* at 8 (citing *C.W. Zumbiel Co. v. Kappos*, 702 F.3d 1371, 1385 (Fed. Cir. 2012)). We agree as explained below.

3. “*A Method for Treating a Hypoxic or Ischemic Disorder or Condition in a Subject*”

We agree with Patent Owner that the preamble is limiting and provides antecedent basis for “the subject” recited in the body of claim 1. The Federal Circuit has stated that

dependence on a particular disputed preamble phrase for antecedent basis may limit claim scope because it indicates a

reliance on both the preamble and claim body to define the claimed invention. Likewise, when the preamble is essential to understand limitations or terms in the claim body, the preamble limits claim scope.

Catalina Marketing Int'l, Inc. v. Coolsavings.com, Inc., 289 F.3d 801, 808 (Fed. Cir. 2002) (citations omitted), cited in *C.W. Zumbiel*, 702 F.3d at 1385; *see also Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003) (“When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention.”).

The preamble of claim 1 describes the purpose of the claimed method is to treat a hypoxic or ischemic disorder or condition in a subject, which gives life and meaning to the claimed method. *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003) (finding preamble’s recitation of the objective of the method gave “life and meaning” to the claim reciting performing the method on someone “in need”).

Such a conclusion is further supported by prosecution history of the ’172 patent as Patent Owner points out. *See* Prelim. Resp. 9–10. Patent Owner points to the Examiner’s reliance on the preamble of claim 1 to distinguish the claimed invention over the art and allow the claims, *id.* (citing Ex. 1016, 5), and Patent Owner’s statements during prosecution relying on the preamble as limiting, *id.* at 10. Petitioner appears to tacitly agree that the preamble is limiting. *See* Pet. 29–30 (stating “Weidmann expressly discloses the administration of a heterocyclic carboxamide compound (e.g., compound of Example 9) in an effective amount (e.g., 1 mg/kg to 10 mg/kg) to a subject (rat) by oral administration *to treat an ischemic condition or disorder* (liver fibrosis)”) (emphasis added); *id.* at 29

n.24 (stating the “’172 patent describes the Bickel tests as showing treatment of liver ischemia”).

For purposes of this decision and based on the record before us, we conclude that the preamble of claim 1 limits the claim to a method for treating a hypoxic or ischemic disorder or condition in a subject, and that the term “the subject” as used in the body of claim 1 refers for antecedent basis to the subject in the preamble that has a hypoxic or ischemic disorder or condition.

B. Principles of Law

A claim is unpatentable under 35 U.S.C. § 102 if a single prior art reference expressly or inherently describes each and every limitation as set forth in the claim. *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1375 (Fed. Cir. 2005); *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987). “A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference.” *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014) (citing *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003)).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). 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 ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In that regard, an obviousness analysis “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR*, 550 U.S. at 418; *see Translogic*, 504 F.3d at 1259. In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person having ordinary skill:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 550 U.S. at 421. “*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless ‘the improvement is more than the predictable use of prior art elements according to their established functions.’” *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We are mindful that the level of ordinary skill in the art also is reflected by the prior art of record.⁵ *See Okajima v. Bourdeau*, 261 F.3d

⁵ Petitioner states that the level of skill in the art at the time of the invention is a person who has a “Ph.D. in physiology or biochemistry (or a related discipline) or an M.D. degree, and one or two years of research experience in cardiology, nephrology, or pulmonology,” which may overlap with the period of education. Pet. 12 (citing Ex. 1002 ¶ 30). Patent Owner does not offer an explicit definition for one of ordinary skill in the art. *See Prelim.*

1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

C. Anticipation by Weidmann

Petitioner contends that claims 1–3, 5, 6, and 8 are unpatentable under 35 U.S.C. § 102(b) as anticipated by Weidmann. Pet. 4; *see* Prelim Resp.

11. Petitioner asserts that

Weidmann expressly discloses the administration of a heterocyclic carboxamide compound (e.g., compound of Example 9) in an effective amount (e.g., 1 mg/kg to 100 mg/kg) to a subject (rat) by oral administration to treat an ischemic condition or disorder (liver fibrosis). While Weidmann does not expressly state that the administered heterocyclic carboxamide compound “stabilizes the alpha subunit of hypoxia inducible factor (HIF α),” upon administration of the compound of Example 9 to treat liver ischemia, HIF- α will be stabilized.

Pet. 29–30 (citing Ex. 1019, 9:61–10:34; Ex. 1002 ¶¶ 94–95).

Patent Owner asserts that this ground fails, among other reasons, because Weidmann does not teach a subject treated for a hypoxic or ischemic disorder and does not inherently teach administering an effective amount of a heterocyclic carboxamide that stabilizes HIF α . Prelim. Resp. 13–28.

Resp. 11–53. We apply Petitioner’s stated level of ordinary skill in the art, which is supported by Dr. Schumacker, because of the sophistication of the technology and the educational level of those who work in this area. *See In re GPAC*, 57 F.3d at 1579.

We agree with Patent Owner that Petitioner has failed to show that it is likely to prevail on its challenge that claims 1–3, 5, 6, or 8 are anticipated by Weidmann.

1. *Weidmann (Ex. 1019)*

Weidmann teaches using substituted isoquinoline-3-carboxamides, which inhibit prolyl-4-hydroxylase, to treat fibrotic disorders. Ex. 1019, 1:8–11. Specifically, Weidmann states that

Compounds which inhibit the enzyme prolyl hydroxylase cause a very selective inhibition of collagen biosynthesis by affecting the collagen-specific hydroxylation reactions. In the course of these, protein-bound proline or lysine is hydroxylated by the enzyme prolyl or lysyl hydroxylase. If this reaction is suppressed by inhibitors, a nonfunctional, underhydroxylated collagen molecule results, which can be released into the extracellular space by the cells only in a small amount. The underhydroxylated collagen additionally cannot be incorporated into the collagen matrix and is very easily proteolytically degraded. As a result of these effects, the amount of extracellularly deposited collagen is decreased overall.

Inhibitors of prolyl hydroxylase are therefore suitable substances in the therapy of disorders in which the deposition of collagens decisively contributes to the clinical picture. These include, inter alia, fibroses of the lung, liver and skin (scleroderma and scarring after burns, injuries and surgical interventions) and also atherosclerosis.

Ex. 1019 1:12–30.

Weidmann further determined the antifibrotic action in the model of carbon tetrachloride-induced liver fibrosis. *Id.* at 9:62–63. To create this model, Weidmann states that “rats were treated twice weekly with CCl₄ (1 ml/kg) dissolved in olive oil. The test substance was administered daily, if appropriate even twice daily, orally or intraperitoneally dissolved in a

suitable compatible solvent.” *Id.* at 9:63–67. Radioimmunological determination of collagen fragments and procollagen peptides in serum was used to assess fibrogenesis activity. *Id.* at 10:4–6. “The compounds according to the invention were active in this model in a concentration of 1 to 100 mg/kg.” *Id.* at 6–8.

2. Analysis

Petitioner asserts that

[f]ollowing the steps set out in Weidmann will result in practicing the methods recited in claim 1 of the ’172 patent, as Weidmann discloses administering a heterocyclic carboxamide compound to a subject to treat ischemic conditions and it is understood that, upon administration of the compound, HIF- α will be stabilized. In essence, the stabilization of HIF- α is the natural flowing result of practicing the disclosure of Weidmann.

Pet. 28 (citing Ex. 1002 ¶¶ 87–96). Therefore, Petitioner concludes that Weidmann inherently teaches stabilization of HIF- α . *See* Pet. 31 (“Because the natural flowing result of practicing Weidmann is the stabilization of the alpha subunit of hypoxia inducible factor (HIF- α), this limitation is inherent within Weidmann’s disclosure.”).

Petitioner supports this assertion by pointing to test data for Compound B in the ’172 patent that Petitioner asserts is the same as the compound of Example 9 of Weidmann. Pet. 23–24. Petitioner concludes that the “testing of Compound B disclosed in Example 1 of the ’172 patent shows that the compound “stabilized HIF α in a normoxic environment in a dose-dependent manner, allowing HIF α to accumulate within the cell.” *Id.* at 23–24 (citing Ex. 1001, 48:59–62).

Although Weidmann explicitly discloses treatment of fibrotic diseases, Petitioner supports the conclusion Weidmann teaches treatment of

ischemic conditions by pointing out that atherosclerosis treated in Weidmann is defined as a chronic ischemic condition in the '172 patent (Pet. 28–29, 29 n.23), and that the model disclosed in Bickel, which Petitioner asserts is the same as taught in Weidmann, is described as treating liver ischemia in the '172 patent (Pet. 23 n. 19, 29 n.24).

Patent Owner asserts that Weidmann does not expressly disclose a subject having an ischemic condition or disorder as Petitioner states, but instead discloses only liver fibrosis (Prelim. Resp. 14–15 (citing Pet. 29–30; Ex. 1002 ¶ 90)), and Petitioner's declarant, Dr. Schumacker, offered no evidence that CCl₄ as used in Weidmann is a "hepatotoxin that induces fibrosis and *liver ischemia*". Nor does Dr. Schumacker cite to any underlying facts or data demonstrating that liver ischemia necessarily results from CCl₄ model used in Weidmann" (Prelim. Resp. 15–16 (citing Ex. 1002 ¶¶ 90–91); *see also* Prelim. Resp. 17–18 (noting Examiner during prosecution of '172 patent distinguished a Weidmann patent with a similar disclosure (*see* Ex. 1002 ¶ 95) regarding inhibiting collagen synthesis and fibrotic diseases and found it was no longer prior art over the invention of the '172 patent that "enabled their heterocyclic compounds as useful in stabilizing HIF- α and useful in treating hypoxic and ischemic related diseases and conditions); Prelim. Resp. 23–25 (discussing '172 patent disclosure that states that ischemia "may" arise from atherosclerosis and other evidence that atherosclerosis does not always result in ischemia); Prelim. Resp. 30 (stating "Petitioner provides no facts or evidence which demonstrate that 'decreasing the extent of liver fibrosis' is equivalent to treating a hypoxic or ischemic disorder or condition").

Patent Owner also states that Petitioner's assertion that Weidmann's liver fibrosis model is the same as the model disclosed in Bickel is incorrect, and Petitioner has not shown that Weidmann's different treatment would result necessarily in the same treatment effects as Bickel. Prelim. Resp. 18–21. Patent Owner points out that “Bickel's model differs in that Weidmann delayed the administration of the test substance for a period of two weeks after the initial administration of CCl₄, whereas Bickel administered the compound ‘*concomitantly* with CCl₄ twice *daily*’,” and “Bickel's model employed a much longer time period (nine weeks) of CCl₄ administration compared with the time period (four weeks) employed in the Weidmann experiment.” Prelim. Resp. 19–20.

Patent Owner also offers evidence that Weidmann's delayed treatment with its test compounds by two weeks after administration of CCl₄ means Weidmann did not treat during the ischemia phase, but only during fibrosis stages of CCl₄ induced liver injury. *Id.* at 21–22. Patent Owner further supports this argument by providing evidence that there are many fibrotic disorders that are not caused by, nor result in, ischemia. *Id.* at 22–23 (citing Exs. 2002–2004).

Lastly, Patent Owner asserts that Petitioner has failed to show any evidentiary support that Weidmann inherently discloses administering “an effective amount of heterocyclic carboxamide that stabilizes . . . HIF α .” Prelim. Resp. 25–28; *see* Prelim. Resp. 26–27 (stating Dr. Schumacker provides no evidence to support his assertions that Weidmann inherently discloses stabilization of HIF α) (citing Ex. 1002 ¶¶ 90–92 and 94–94). Specifically, Patent Owner asserts that conditions and dosages used to test

Compound B in the '172 patent are different from those for Compound 9 in Weidmann. *Id.* at 27–28.

We agree with Patent Owner that Petitioner has failed to show a reasonable likelihood of success that any of claims 1–3 5, 6, or 8 are anticipated by Weidmann. Weidmann addresses treatment of fibrosis and selective inhibition of collagen synthesis and does not discuss or even mention hypoxic or ischemic conditions. *See generally* Ex. 1019. Petitioner paints with too broad a brush in attempting to establish that Weidmann inherently discloses administering an effective amount of heterocyclic carboxamide compound that stabilizes the alpha subunit of HIF α to a subject with a hypoxic or ischemic disorder or condition.

Petitioner's anticipation analysis hinges on equating Weidmann's liver fibrosis model with liver ischemia, and assuming that inhibition of collagen synthesis with substituted isoquinoline-3-carboxamides taught in Weidmann would necessarily result in administering an effective amount of heterocyclic carboxamide to inhibit HIF prolyl hydroxylase, and thus, stabilize HIF α . Petitioner has not provided convincing evidence to establish these assumptions. *See* Ex. 1002 ¶¶ 88–101. Specifically, Petitioner relies on the fact that Weidmann discloses the same or similar heterocyclic carboxamides as taught by the '172 patent, and makes the leap that Weidmann must inherently teach the methods as claimed in the '172 patent. Such is not necessarily so.

For instance, Petitioner offers insufficient evidence that Weidmann's CCl₄ model of liver fibrosis also necessarily creates an ischemic condition. Petitioner points to the '172 patent disclosure in which Bickel is described as displaying a model of toxic-ischemic livery injury and concluding that CCl₄

is a model of toxic-ischemic liver injury. *See* Ex. 1002 ¶ 90 n.8. Petitioner makes no effort to show that Weidmann’s application of CCl₄ is the same as Bickel’s, *see* Ex. 1002 ¶ 64 n.5 (stating simply that Weidmann’s induction of liver fibrosis “is the same ischemia model used in Bickel”), and Patent Owner points out that it is not. *See* Prelim. Resp. 18–21. Patent Owner also offers evidence that Weidmann’s delay in administering the subject compound missed any ischemic phase of CCl₄-induced liver injury, and not all fibrotic disorders entail ischemia. *See* Prelim. Resp. 21–23.

Petitioner also relies on Weidmann’s recitation of the level of activity for the prolyl hydroxylase inhibitors in its model for decreasing the extent of liver fibrosis as providing an effective amount for the claimed invention. *See* Pet. 29. Again, Petitioner does not support adequately the conclusion that such activity would equate to an effective amount of heterocyclic carboxamide to treat a subject with a hypoxic or ischemic disorder or condition. *See* Ex. 1002 ¶¶ 88–101 (lacking discussion of “an effective amount”).

We find that Petitioner has failed to show that it has a reasonable likelihood of prevailing on any of claims 1–3, 5, 6, or 8 as anticipated by Weidmann.

D. Obviousness over Ivan and Bickel, Alone or in Combination with Weidmann or Semenza

Petitioner contends that claims 1–3, 5, and 6 are unpatentable under 35 U.S.C. § 103 as obvious over Ivan and Bickel. Pet. 2, 37–44. Petitioner states “[i]n particular, [claim 1] is obvious in light of (1) the disclosure by Ivan 2001 that inhibitors of prolyl hydroxylase inhibitors could stabilize HIF- α and be useful in treating conditions where it is desirable to modulate

HIF, including ischemia, and (2) Bickel 1998, which teaches the use of heterocyclic carboxamide compound that inhibits prolyl hydroxylase in the treatment of liver ischemia.” Pet. 37 (citing Ex. 1002 ¶¶ 103–107).

Petitioner posits that one of skill in the art would have been motivated to combine the teachings of the two references because Ivan invites testing of heterocyclic carboxamide prolyl hydroxylase inhibitors of Bickel against ischemic conditions and disorders. *Id.* (citing Ex. 1025, 467, 468 n.32).

Patent Owner counters that Petitioner failed to explain why Ivan and Bickel disclose an effective amount of heterocyclic carboxamide to stabilize HIF α in a subject having a hypoxic or ischemic disorder or condition, and failed to consider the teachings of Ivan and Bickel as a whole suggesting that a person of skill in the art would not have had a reasonable expectation of success of stabilizing HIF α in a subject having a hypoxic or ischemic order or condition. Prelim. Resp. 3–4.

We agree with Patent Owner that Petitioner has failed to show that it is likely to prevail in its challenge that claims 1–3, 5 or 6 are obvious over Ivan and Bickel.

1. *Ivan (Ex. 1025)*

Ivan discussed an investigation of the mechanism by which hypoxia prevents the destruction of HIF. Ex. 1025, 464. Ivan states that “[i]n mammalian cells, lack of oxygen, or hypoxia, leads to the stabilization of a sequence-specific DNA binding transcription factor called HIF, which transcriptionally activates a variety of genes linked to processes such as angiogenesis and glucose metabolism.” *Id.* In contrast, Ivan states that in the presence of oxygen, the von Hippel-Lindau tumor suppressor protein (pVHL), along with elongin B and C, binds directly to HIF α subunits

targeting them for polyubiquitination and destruction by the E3 ubiquitin ligase that contains the pVHL. *Id.*

In studying the mechanism by which destruction of HIF is accomplished, Ivan found that “human pVHL binds to a short HIF-derived peptide when a conserved proline residue at the core of this peptide is hydroxylated.” *Id.* at Abstract. In evaluating the proline hydroxylation requirement for the destruction of HIF, Ivan also speculated that HIF hydroxylation is carried out by an enzyme. *Id.* at 467.

In discussing the findings, Ivan acknowledges the complicated nature of the mechanism for HIF hydroxylation, stating:

The pVHL binding peptide present in HIF does not closely resemble the naturally occurring or synthetic prolyl hydroxylation targets identified to date. Moreover, HIF is intracellular, whereas the majority of proline hydroxylase activity is associated with the endoplasmic reticulum where it is required for normal collagen biosynthesis. It is therefore unlikely that HIF is modified by the type I and type II prolyl 4-hydroxylases.

The requirement of molecular oxygen and iron for proline hydroxylase activity would potentially explain the stabilization of HIF observed under hypoxic conditions or after treatment with agents that eliminate or compete with iron. This notion, however, may be oversimplified. First, the prolyl hydroxylases that modify collagen are active in hypoxic cells. Second, earlier studies indicated that oxygen sensing involved changes in reactive oxygen species, protein phosphorylation, and protein nitrosylation. Conceivably, these changes directly or indirectly affect the hydroxylation of HIF. Finally, our findings do not provide an immediate explanation for the observation that hypoxic induction of HIF is prevented in the presence of heme inhibitors such as carbon monoxide.

Id. at 467.

Ivan does recognize a potential for treatment of ischemic conditions. Ivan states:

Tissue ischemia is a major cause of morbidity and mortality. In principle, drugs that stabilize HIF may augment angiogenesis and the adaptation to chronic hypoxia. Several small-molecule proline hydroxylase inhibitors have been developed as antifibrotic agents and can now be tested in ischemia models [citing Bickel].

The activation of HIF by hypoxia is complex and involves changes in protein stability, nuclear localization, DNA binding capability, and transcriptional activation function. The knowledge that proline hydroxylation govern HIF turnover in the presence of oxygen should facilitate dissection of the mechanisms underlying these various aspects of HIF regulation.

Id. (citations omitted).

2. *Bickel (Ex. 1027)*

Bickel demonstrated the antifibrotic activity of S 4682, an inhibitor of prolyl 4-hydroxylase, in a long-term experiment inducing liver fibrosis in rats by chronic application of CCl₄. Ex. 1027, 404. The experiments disclosed in Bickel were described in the '172 patent as follows:

Bickel et al. (1998; Hepatology 28:404-411) reported the use of a compound of the invention following induction of toxic-ischemic injury in the liver. Although the authors interpreted their results relative to the effect of the compounds on fibrosis, the authors acknowledged that the beneficial effects on variables of liver function including serum levels of bilirubin, bile acids, and alkaline phosphatase could not be directly attributed to a reduction in fibrosis.

Ex. 1001, 59:12–40.

3. *Analysis*

Petitioner sets forth its challenge as follows:

Considering that Ivan 2001 teaches the administration of a compound that inhibits prolyl hydroxylase to result in the

stabilization of HIF- α and suggests the testing of the heterocyclic compounds of Bickel 1998 in ischemia models as potentially effective in angiogenesis and the adaption to chronic hypoxia, a person of ordinary skill in the art, as of the effective filing date of the '172 patent, would have a reasonable expectation that a heterocyclic carboxamide compound would (i) stabilize HIF- α and (ii) treat a subject suffering from a hypoxic or ischemic condition or disorder.

Pet. 39.

Patent Owner counters that Petitioner has failed to show that Ivan and Bickel disclose or suggest “an effective amount” of heterocyclic carboxamide to treat a subject having a hypoxic or ischemic disorder or condition. Prelim. Resp. 32. Specifically, Patent Owner asserts that Petitioner provides no explanation why the amount of S 4682 used in Bickel’s experiment for treating fibrosis, is an effective amount for stabilizing HIF α in a subject having a hypoxic or ischemic disorder or condition. *Id.* at 34.

Patent Owner also asserts that a person of ordinary skill would not have had a reasonable expectation of success of stabilizing HIF α in a subject having a hypoxic or ischemic disorder or condition. *Id.* at 35. Patent Owner points out that Petitioner admits that Ivan “does not discuss that a heterocyclic carboxamide can be utilized to inhibit prolyl hydroxylase to result in the stabilization of HIF- α .” *Id.* (quoting Pet. 38).

Patent Owner also asserts that Petitioner fails to account for the teachings of Ivan and Bickel as a whole. *Id.* at 37–45. Patent Owner asserts that in light of Bickel’s focus on reducing fibrosis through targeting collagen and on inhibiting collagen prolyl hydroxylase in liver-specific fibrosis, and in light of Ivan’s teaching that it is unlikely that HIF α is regulated by compounds that inhibit collagen-regulating prolyl hydroxylases and the

unpredictable and complex nature of HIF activity regulation, one of skill in the art would not have a reasonable expectation of success in arriving at the claimed invention. *Id.* at 44–45.

We agree with Patent Owner that the teachings of the combination of Ivan and Bickel do not teach or suggest the claimed invention. For instance, Bickel addresses treatment of fibrosis and does not specifically address the use of heterocyclic carboxamides for the treatment of a subject with a hypoxic or ischemic disorder or condition, and therefore, does not teach or suggest an appropriate effective amount of heterocyclic carboxamides for treating such condition. *See generally* Ex. 1027. The characterization of Bickel in the '172 patent as set forth above does not indicate that Bickel teaches or suggests such an effective amount as the '172 patent merely acknowledged that Bickel disclosed beneficial effects on variables of liver function that could not be directly attributed to a reduction in fibrosis. *See* Ex. 1001, 59:19–24.

We also agree with Patent Owner that one of skill in the art would not have a reasonable expectation of success in arriving at the claimed invention based on the combination of Ivan and Bickel. *See Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (stating one may show obviousness of a claim by showing “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 from doing so.”) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)). Ivan’s suggestion that several small-molecule proline hydroxylase inhibitors, including Bickel’s S 4682, developed as antifibrotic agents “can now be tested in ischemia

models” does not provide a reasonable expectation of success that Bickel’s teachings regarding his proline hydroxylase inhibitor would result in the claimed invention of an effective amount to stabilize the alpha subunit of HIF α to treat a hypoxic or ischemic disorder or condition in a subject.

This is especially true in light of Ivan’s questions concerning what type of prolyl hydroxylase would hydroxylate the appropriate proline residue in HIF α , *see* Ex. 1025, 467, or Ivan’s explanation of the complexity of the activation of HIF by hypoxia, *see id.* The remaining claims in the challenge using Ivan and Bickel, claims 2, 3, 5, and 6, depend either directly or indirectly from claim 1. Therefore, Petitioner has also failed to show a reasonable likelihood of success in showing claims 2, 3, 5, and 6 are unpatentable under this challenge also. *See In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) (“If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious.”).

Petitioner also asserts that claim 8 is unpatentable under 35 U.S.C. § 103(a) as obvious over Ivan, Bickel, and Weidmann, and that claims 4 and 7 are unpatentable under 35 U.S.C. § 103(a) as obvious over Ivan, Bickel, and Semenza. Concerning claim 8, Petitioner uses Weidmann to teach oral administration of the heterocyclic carboxamide compound, Pet. 45–46, and relies on the combination of the teachings of Ivan and Bickel to teach the remaining limitations as described above. For the reasons that we stated above, this challenge to claim 8 also fails.

As to the Petitioner’s last challenge to claims 4 and 7 of the ’172 patent, Petitioner again relies on the combination of the teachings of Ivan and Bickel as set forth above to teach the limitations of claim 1 from which

claims 4 and 7 ultimately depend,⁶ and add the limitations of “wherein the ischemic event is acute” and “wherein the hypoxic or ischemic disorder or condition is associated with ischemic reperfusion injury in a subject,” respectively. Ex. 1001, 63:42–43, 64:37–39. Petitioner adds Semenza to the challenge to teach these additional limitations. Pet. 46–49. For the reasons set forth above with respect to claim 1, this challenge also fails. *See* Prelim. Resp. (stating with regard to the challenge for claim 8 that disclosure of oral administration of a heterocyclic carboxamide compound does not cure the deficiencies of Ivan and Bickel); *id.* at 46–49 (stating that claims 4 and 7 are not unpatentable for at least the reasons provided for claim 1 and challenging Petitioner’s characterization of the teachings of Semenza).

We find that Petitioner has failed to show that it has a reasonable likelihood of prevailing on any of claims 1–8 based on the combination of Ivan and Bickel, either alone or in combination with Weidmann or Semenza.

III. CONCLUSION

After reviewing the information presented in the Petition and the Preliminary Response, as well as the evidence of record, we determine that Petitioner has not established a reasonable likelihood that it will prevail in showing that any of claims 1–8 of the ’172 patent are unpatentable.

⁶ Claim 3 from which claim 4 depends adds the following limitation to claim 1, “wherein the hypoxic or ischemic disorder or condition is associated with an ischemic event.” Ex. 1001, 63:40–41. Petitioner relies on Ivan’s general statement about an invitation to test small-molecule proline hydroxylase inhibitors in ischemia models and Bickel’s teaching of using such a proline hydroxylase to treat fibrosis. As explained above with regard to claim 1, these teachings fall short.

IV. ORDER

Accordingly, it is

ORDERED that the Petition is *denied* as to all challenged claims of the '172 patent.

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