

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE OFFICE OF THE UNDER SECRETARY OF COMMERCE
FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE
UNITED STATES PATENT AND TRADEMARK OFFICE

NEUROCRINE BIOSCIENCES, INC.,
Petitioner,

v.

SPRUCE BIOSCIENCES, INC.,
Patent Owner.

PGR2021-00088
Patent 10,849,908 B2

Before KATHERINE K. VIDAL, *Under Secretary of Commerce for
Intellectual Property and Director of the United States Patent and
Trademark Office.*

DECISION

Vacating the Decision Denying Institution and Remanding to the Patent
Trial and Appeal Board Panel for Further Proceedings

I. INTRODUCTION

Neurocrine Biosciences, Inc. (“Petitioner”) filed a Petition (Paper 3, “Pet.”)¹ requesting a post-grant review of claims 1–25 of U.S. Patent No. 10,849,908 B2 (Ex. 1001, “the ’908 patent”). Spruce Biosciences, Inc. (“Patent Owner”) filed a Preliminary Response (Paper 8, “Prelim. Resp.”).

Petitioner challenges claims 1–4, 7–9, 11–14, 17–19, and 21–24 under 35 U.S.C. § 102 as inherently anticipated by Grigoriadis.² Pet. 3. Petitioner challenges claims 4, 10, 14, 20–22, and 25 under 35 U.S.C. § 103 as obvious over Grigoriadis, and claims 5, 6, 15, and 16 under 35 U.S.C. § 103 as obvious over Grigoriadis and Romano.³ *Id.* at 3–4. Additionally, Petitioner challenges claims 1–25 under 35 U.S.C. § 112(a) as lacking written description and enablement. *Id.* at 4. For example, Petitioner argues that the ’908 patent broadly claims using a genus of compounds to treat congenital adrenal hyperplasia (“CAH”), but the ’908 patent specification describes treating CAH with only a single compound within the genus. *Id.* at 2–3. Petitioner argues that the ’908 patent specification does not provide written description support for the broad claims. *Id.*

On December 10, 2021, the Patent Trial and Appeal Board (“Board”) denied institution of a post-grant review of the ’908 patent. Paper 11 (“Decision” or “Dec.”). The Board rejected each of Petitioner’s proposed grounds of unpatentability, including those based on inherent anticipation of

¹ Paper 3 is the public version of the Petition and Paper 2 is the confidential version. Citations to the Petition are to the public version unless otherwise noted.

² U.S. Patent Application Publication No. US 2017/0020877 A1 (Ex. 1006).

³ U.S. Patent Application Publication No. US 2005/0209250 A1 (Ex. 1007).

the challenged claims by Grigoriadis and on lack of written description support for the challenged claims. *See* Dec. 13–21, 26–31.

On January 10, 2022, Petitioner filed a rehearing request and a request for Precedential Opinion Panel (“POP”) review. *See* Papers 12 (“Reh’g Req.”), 13; Ex. 3001. In the request for POP review, Petitioner argued that:

Precedential Opinion Panel review is warranted to ensure that a uniform legal standard is applied when assessing the patentability of method of treatment claims, and to correct the Board’s errors of law in analyzing inherent anticipation and written description.

Ex. 3001, 2.

On July 20, 2023, I issued an order granting *sua sponte* Director Review (Paper 14) and the POP dismissed the request for POP review (Paper 15).

For the reasons set forth below, I vacate the Board’s Decision denying institution of post-grant review, and remand to the Board for further proceedings consistent with this decision.

II. BACKGROUND

The ’908 patent relates to a method for treating congenital adrenal hyperplasia (“CAH”), a hormone disorder that may result in elevated levels of some hormones (e.g., adrenocorticotrophic hormone (“ACTH”) and 17-hydroxyprogesterone (“17-OHP”)), and insufficient levels of other hormones (e.g., cortisol). Ex. 1001, 1:35–38, 11:49–12:26. This resulting hormone imbalance may cause severe disease. *See id.* at 10:66–11:48; *see* Ex. 1005 ¶ 21. Conventional treatments of CAH, such as long-term administration of glucocorticoids or mineralcorticoids, may result in numerous side effects. *See* Ex. 1001, 10:66–11:48; *see* Ex. 1005 ¶ 21.

The '908 patent specification describes a method for treating CAH by administering a compound that interferes with the binding of corticotropin releasing factor (“CRF”) with its corresponding CRF receptor (subtype 1) (“CRF₁”). *See* Ex. 1001, 11:49–64; *see* Ex. 1005 ¶ 23. Such compounds are known as CRF₁ receptor antagonists. *See* Ex. 1001, 11:57–64. The '908 patent notes that at the time of filing of the patent application, CRF₁ receptor antagonists previously had been reported and there was ongoing research and development into small molecule CRF₁ receptor antagonists and their therapeutic use. *See id.* at 10:47–65, 11:57–64. The '908 patent specifically identifies one CRF₁ receptor antagonist useful for treating CAH, Compound 1, i.e., 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine. *Id.* at 12:27–31, 14:15–42. Compound 1 is also known as tildacerfont. Pet. 11 (citing Ex. 1005 ¶ 31; Ex. 1011, 1).

The specification further discloses various methods for treating CAH by administering tildacerfont, and describes results from a clinical trial of administering tildacerfont to treat CAH in human patients. Ex. 1001, 26:11–33:53. The claims in the '908 patent are directed to methods for treating CAH in a human by administering a therapeutically-effective amount of a CRF₁ receptor antagonist or salt thereof, wherein an ACTH or 17-OHP level “in the human is reduced by at least 10% from baseline.” *Id.* at 48:6–49:15 (claims 1–25).

III. ANALYSIS

A. Anticipation

In the Petition, Petitioner argues that Grigoriadis discloses a method of treating CAH by administering (SSR-125543) crinecerfont, a CRF₁ receptor antagonist. Pet. 30, 46–48 (citing Ex. 1006 ¶ 54; Ex. 1005 ¶¶ 28,

53). Grigoriadis lists various embodiments of CRF₁ receptor antagonists useful for treating CAH, including NBI-77860 (verucerfont) and SSR-125543 (crinecerfont), among other compounds. Ex. 1006 ¶¶ 51, 54, 66; Ex. 1005 ¶¶ 28, 53. Grigoriadis discloses a single clinical study for treating CAH by administering verucerfont. *See* Ex. 1006 ¶¶ 90–93.

Petitioner argues that administering crinecerfont to a human to treat CAH, as disclosed in Grigoriadis, inherently provides the '908 patent's claimed results of reducing ACTH and 17-OHP levels by at least 10% from baseline. Dec. 13 (citing Pet. 47). As evidence of the inherent properties of administering crinecerfont to treat CAH, Petitioner submitted test results from a confidential, non-prior art clinical study, Auchus.⁴ Dec. 13–14, 17–18 (citing Pet. 30–31; Ex. 1005 ¶¶ 54–62; Ex. 1009, 10, 13–19, Figs. 1–2, Table 2).

The Board determined that Petitioner failed to establish that it is more likely than not that Grigoriadis anticipates independent claims 1 and 11. Dec. 16–20. The Board found that, although Grigoriadis discloses crinecerfont as a CRF₁ receptor antagonist, Grigoriadis does not disclose crinecerfont as a study drug in a clinical trial for treating CAH. *Id.* at 19. Rather, the Board found that Grigoriadis mentioned crinecerfont “only as being one of a class of CRF_[1] receptor antagonists.” *Id.* By contrast, the confidential non-prior art clinical study by Auchus specifically employed crinecerfont as the study drug in its clinical trial. *Id.*; Ex. 1009. The Board determined, however, that “Petitioner may not attempt to import

⁴ R.J. Auchus et al., *Crinecerfont Lowers Elevated Biomarkers of Disease Control in Adults with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency*, a manuscript that has been submitted for review for publication in *The Lancet*. Ex. 1009.

experimental results from Auchus that are not prior art to the '908 patent in an attempt to show that crinecerfont inherently has clinical properties that were not already demonstrated in Grigoriadis.” Dec. 19. The Board also determined that Petitioner’s inherency argument was not commensurate with the scope of the claims because “Petitioner has not demonstrated that all, or even a representative number of th[e] genus [of over 100 CRF₁ receptor antagonists] have necessarily demonstrated an ‘at least 10% reduction in a patient’s ACTH level from baseline.’” *Id.* at 20.

In its rehearing request, Petitioner asserts, *inter alia*, two errors in the Board’s anticipation analysis. Reh’g Req. 7–13. First, Petitioner argues that the Board did not apply the correct legal standard when it required that Petitioner demonstrate that a representative number of CRF₁ receptor antagonists meet the claimed limitations of reducing ACTH level from baseline, to show it is more likely than not that the challenged claims are anticipated. *Id.* at 8–10. According to Petitioner, “it is black letter law that a genus claim limitation is anticipated by a single prior art species.” *Id.* at 9 (citing *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001)). Petitioner argues that “[u]nder the correct legal standard, Grigoriadis’[s] disclosure of administering crinecerfont, a species in the genus of CRF_[1] receptor antagonists that inherently results in the recited ACTH or 17-OHP reductions, anticipates claims 1 and 11.” *Id.* (citing *Eli Lilly.*, 251 F.3d at 971)).

Second, Petitioner argues that the Board legally erred by rejecting Petitioner’s experimental results from Auchus to show the inherent properties of administering crinecerfont for treating CAH. *Id.* at 10–11. Petitioner argues that the Board’s treatment of Auchus “is contrary to Federal Circuit precedent holding ‘extrinsic evidence can be used to

demonstrate what is “necessarily present” in a prior art embodiment even if the extrinsic evidence is not itself prior art.” *Id.* at 10 (citing *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020)). I address Petitioner’s arguments in turn.

1. *Grigoriadis Discloses Administering Crinecerfont to Treat CAH*

First, I address whether Grigoriadis’s disclosure of a method of treating CAH by administering crinecerfont can anticipate the broader genus of treating CAH by administering a CRF₁ receptor antagonist. A reference is anticipatory if it discloses every limitation of the claimed invention either explicitly or inherently. *Eli Lilly*, 251 F.3d at 970 (Fed. Cir. 2001) (citing *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999) (“[I]f granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated, regardless of whether it also covers subject matter not in the prior art.”)). Federal Circuit “case law firmly establishes that a later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim.” *Id.* at 971; *see also In re May*, 574 F.2d 1082, 1089–1090 (CCPA 1978) (finding “technical anticipation” where the prior art disclosed achieving the claimed function by administering a species within the claimed genus). In *Eli Lilly*, for example, the Federal Circuit found an earlier patent claiming administering fluoxetine hydrochloride to humans for treating anxiety inherently anticipated a later claim to administering fluoxetine hydrochloride to animals. *Id.* at 969, 971. Specifically, the Federal Circuit found that the prior art species, humans, anticipated the claimed genus, animals, noting that “[h]umans are a species of the animal genus.” *Id.* at 971; *see also May*, 574 F.2d at 1089 (“May expressly discloses the hydrobromide salt of *(-)-2'-hydroxy-2,5,9-trimethyl-*

6,7-benzomorphan, which appellants admit is a species within the genus of claim 1.”).

Grigoriadis describes a method of treating CAH by administering crinecerfont. Ex. 1006 ¶¶ 21, 53, 54, 66. Grigoriadis discloses that crinecerfont is a species of the genus of CRF₁ receptor antagonists, among other CRF₁ receptor antagonists. *Id.* ¶ 54. The Board found that crinecerfont was “mentioned only as being one of a class of CRF_[1] receptor antagonists.” Dec. 19. Nevertheless, a reference may still anticipate even if it lists the anticipatory compound among a longer list without special emphasis. *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005). In *Perricone*, the Federal Circuit found that the specific disclosure of ascorbyl palmitate, among fourteen other active compounds administered to the skin, inherently anticipated later claims reciting methods of achieving particular skin benefits with the same compound. *Id.* at 1376, 1378. The court held that the reference disclosing ascorbyl palmitate in a list without special emphasis was “prior art to the extent of its enabling disclosure.” *Id.* at 1376. Notably, the court held that the “disclosure, even in a list, makes this case different from cases involving disclosure of a broad genus without reference to the potentially anticipating species.” *Id.* at 1377.

Under applicable Federal Circuit law, Grigoriadis’s method of treating CAH by administering crinecerfont anticipates the broader genus claim of treating CAH by administering a CRF₁ receptor antagonist, so long as the remaining limitations are disclosed expressly or inherently. I vacate the Board’s determination otherwise, and remand for further consideration consistent with this Decision.

2. *Auchus as Evidence of Inherency*

Second, I examine whether the Board legally erred by failing to consider Auchus as evidence of the inherent properties of Grigoriadis's method of treating CAH by administering crinecerfont, and specifically whether use of crinecerfont in Grigoriadis's method necessarily reduces an ACTH or 17-OHP level in a human "by at least 10% from baseline." Ex. 1001, 48:6–49:15 (*see, e.g.*, independent claims 1 and 11); *see also, e.g.*, Dec. 13–16 (citing Pet. 47–48, 54–58 (alleging that Grigoriadis inherently results in an at least 10% reduction of the patient's ACTH or 17-OHP level compared to the patient's baseline)). The Federal Circuit has held that "[e]xtrinsic evidence can be used to demonstrate what is 'necessarily present' in a prior art embodiment even if the extrinsic evidence is not itself prior art." *Hospira*, 946 F.3d at 1329. The court explained that "[t]he later evidence is not itself prior art; it only helps to elucidate what the prior art consisted of." *Id.* at 1330.

In the Decision denying institution, the Board faulted Petitioner for attempting to "import experimental results from Auchus that are not prior art to the '908 patent" in an attempt to show inherent anticipation by Grigoriadis. Dec. 19. The Board failed to appreciate that Petitioner was not relying on Auchus as prior art itself, but as evidence to elucidate the inherent characteristics of Grigoriadis's disclosed method. Thus, I find the Board erred in stating that Petitioner may not rely on results from Auchus as evidence of inherent properties of crinecerfont because Auchus itself is not prior art. *Id.*

Accordingly, I vacate the Board's Decision disregarding Auchus as later evidence of what is necessarily present in Grigoriadis. The preliminary record before me indicates that Auchus shows that the process of

administering crinecerfont (a CRF₁ receptor antagonist) to treat CAH, as disclosed in Grigoriadis, inherently results in the reduced levels of ACTH or 17-OHP recited in independent claims 1 and 11 of the '908 patent. To the extent the Board disregarded Auchus because it did not replicate Grigoriadis's study, I vacate the Board's analysis and remand for further consideration consistent with this Decision.

On remand, the Board should recognize that claims 1 and 11 do not include any further limitations other than treating CAH by administering a CRF₁ receptor antagonist resulting in the claimed reduction of ACTH or 17-OHP from baseline. *See Hospira*, 946 F.3d at 1330 (finding that importing limitations into the claim for the inherency analysis would be improper). In particular, claims 1 and 11 do not require any specific CRF₁ receptor antagonist, or any specific dosing amount or regimen for treating CAH with a CRF₁ receptor antagonist.

B. Written Description

In the Petition, Petitioner argues that “the claims of the '908 patent fail the written description requirement because the '908 patent does not show possession of the claimed subject matter.” Pet. 72. Petitioner argues that the claims are broadly drawn to treating CAH by administering a CRF₁ receptor antagonist, and that “CRF₁ receptor antagonists represent a large, structurally diverse class of over 100 compounds.” *Id.* at 72–73. In contrast, the '908 patent discloses administering a single CRF₁ receptor antagonist, tildacerfont, for treating CAH. *Id.* Petitioner further argues that the '908 patent does not disclose “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 74; *see Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (“[T]he court’s written description

doctrine has always expressly permitted the disclosure of structural features common to the members of the genus.”).

The Board determined that Petitioner failed to establish that it is more likely than not that the claims of the '908 patent lack written description in the specification. Dec. 28–30. The Board found that “[t]he challenged claims recite a genus (‘a CRF₁ receptor antagonist or pharmaceutically acceptable salt thereof[’]) that is not itself claimed. The claims, rather, are directed to a method of using that genus in the treatment of CAH.” *Id.* at 29. The Board further found that the '908 patent specification: (1) disclosed that CRF₁ receptor antagonists were known in the art, (2) identified an example of a CRF₁ receptor antagonist, and (3) provided an exemplary embodiment of administering a CRF₁ receptor antagonist to achieve the claimed effect. *Id.* (citing Ex. 1001, 10:47–64, 12:27–30, Example 4). Finally, the Board found that the prior art and Petitioner’s expert declarant, Dr. Carey, described the genus of CRF₁ receptor antagonists as well known in the art at the time of the invention. *Id.* at 29–30 (citing Ex. 1006 ¶¶ 20, 21, 25, 26, 52–55; Ex. 1005 ¶ 99).

Petitioner argues in the rehearing request that the Board’s Decision “is contrary to Federal Circuit precedent governing written description analysis.” Reh’g Req. 14. Petitioner argues that “[w]hether it would have been obvious to use a known class of compounds to treat CAH is not the issue. Rather, the issue is what the patent itself would convey to a person of ordinary skill.” *Id.* at 15 (citing *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571–72 (Fed. Cir. 1997)). Petitioner argues that the patent itself only conveys administering tildacerfont to treat CAH with the claimed effects, as opposed to using the entire genus of CRF₁ receptor antagonists. *Id.* (citing Ex. 1005 ¶¶ 98–100).

I agree that the Board's Decision is contrary to Federal Circuit precedent. "[S]ufficient description of a 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." *Ariad*, 598 F.3d at 1350 (quoting *Eli Lilly*, 119 F.3d at 1568–69); *see also AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014) ("Functionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus.").

The preliminary record before me indicates that Petitioner sufficiently establishes that the '908 patent specification does not describe *any* structure, formula, or chemical name for the genus of CRF₁ receptor antagonists, and discloses only one particular species, that may be administered to treat CAH and cause a 10% reduction in ACTH or 17-OHP, as claimed. *See* Ex. 1001, 10:47–65, 11:58–64. In *Ariad*, the Federal Circuit found that the "claims here recite methods encompassing a genus of materials achieving a stated useful result But the specification does not disclose a variety of species that accomplish the result." 598 F.3d at 1350. Likewise, on this preliminary record, Petitioner sufficiently establishes that the '908 patent claims methods encompassing a genus of materials achieving stated results, but the specification does not disclose a variety of species that accomplish the results. Petitioner also sufficiently establishes at this time that the '908

patent does not describe structural features common to all species within the genus that accomplish the claimed results.

Although Petitioner's declarant and the prior art describe CRF₁ receptor antagonists as well-known, I do not agree with the Board's finding that the '908 patent specification itself supports claims to the entire class of CRF₁ receptor antagonists that can be used to treat CAH and result in the claimed 10% reduction of ACTH or 17-OHP. *See* Dec. 29–30. In briefing before the Board, Patent Owner acknowledges that other species within the genus do not achieve the same results. *See* Prelim. Resp. 31–34 (arguing that results of a trial study conducted using a different species and under different methods than the study disclosed in Grigoriadis cannot be relied on for inherency). Similarly, as noted above, based on the record before me, Petitioner sufficiently establishes that the '908 patent does not describe structural features common to all species within the genus of CRF₁ receptor antagonists that could be administered to treat CAH and result in a 10% reduction in ACTH or 17-OHP, so as to demonstrate possession of the method of treating CAH broadly claimed. The specification thus “provides no method of distinguishing effective from ineffective compounds for the compounds reaching beyond” the one single compound disclosed in the '908 patent. *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019). Accordingly, Petitioner sufficiently establishes at this time that the '908 patent specification fails to disclose “a representative number of species falling within the scope of the genus or structural features common to the members of the genus.” *Id.* (quoting *Ariad*, 598 F.3d at 1350).

The Board erred in dismissing these shortcomings based on the disclosure of a single compound because “the genus of CRF_[1] receptor

antagonists was well known in the art at the time of invention.” Dec. 29–30. The ’908 patent claims recite methods of treating a condition by administering a broad genus of compounds. Description of a single compound in the genus or knowledge generally of the genus’ members, without more, is insufficient to demonstrate possession of such broad method claims. The specification must provide some way to distinguish effective from ineffective compounds among those encompassed by the broad genus of compounds so claimed. *See Idenix*, 941 F.3d at 1165 (“[T]he specification provides no indication that any nucleosides outside of those disclosed in its formulas could be effective to treat HCV—much less any indication as to *which* of those undisclosed nucleosides would be effective.”).

Having made these factual determinations, I vacate the Board’s written description analysis and remand to the Board for further consideration consistent with this Decision.

IV. CONCLUSION

I find, as to anticipation, that Petitioner has shown on this preliminary record that the prior art (Grigoriadis) discloses a method of treating CAH by administering a species of CRF₁ receptor antagonist (crinecerfont) within the claimed genus. Accordingly, I remand to the Board to determine whether Petitioner’s extrinsic evidence (Auchus) shows that crinecerfont inherently (necessarily) reduces the level of ACTH or 17-OHP “by at least 10% from baseline” when used as taught in Grigoriadis’s method of treating CAH, and thereafter determine whether Petitioner has established that it is more likely than not that Grigoriadis anticipates the challenged claims.

I further find, as to written description, that Petitioner has shown on this preliminary record that the '908 patent specification does not disclose a representative number of species falling within the scope of the recited genus of CRF₁ receptor antagonists that can be used in the claimed method to treat CAH and cause a 10% reduction in ACTH or 17-OHP. Likewise, I find that Petitioner has shown on this preliminary record that the '908 patent specification does not disclose structural features common to the members of the functional genus so that one of skill in the art can visualize or recognize the effective members of the genus of CRF₁ receptor antagonists. Having made these factual determinations, I remand to the Board to proceed consistent with this Decision.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Board's Decision denying institution is vacated;
and

FURTHER ORDERED that the case is remanded to the Board for further proceedings consistent with this Decision.

PGR2021-00088
Patent 10,849,908 B2

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