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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JOSEPH K. BELANOFF

Appeal 2020-005311
Application 14/020,205
Technology Center 1600

BEFORE DONALD E. ADAMS, ULRIKE W. JENKS, and TAWEN CHANG, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from Examiner's decision to reject claims 1, 15, 17–26, and 28–33 (*see* Appellant's July 13, 2020 Reply Br. 2).[2] We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as "Corcept Therapeutics, Inc." (Appellant's February 3, 2020 Appeal Brief (Appeal Br.) 3).

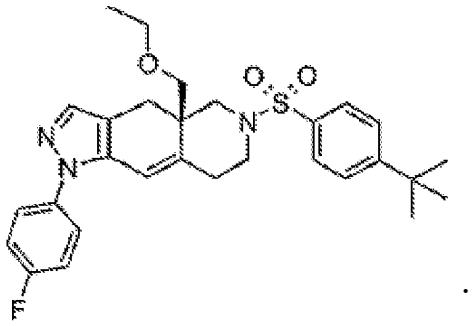
[2] Appellant's Appeal Brief includes claim 27 in its listing of the claim status (*see* Appeal Br. 5). We note, however, that Appellant's Reply Brief correctly excludes claim 27 from the status of the claims (*see* Reply Br. 2; *see also* Appellant's July 2, 2019 Response 5 ("Claim 27 has been

STATEMENT OF THE CASE

Appellant's disclosure "relates to the discovery that an agent capable of antagonizing the binding of cortisol to a glucocorticoid receptor is useful in methods for treating a patient diagnosed with Amyotrophic Lateral Sclerosis (ALS)." (Spec. ¶ 2).

During prosecution Examiner required Appellant to elect, for examination purposes, "one particular non-[steroidal] glucocorticoid receptor specific antagonist (complete with chemical name and structure)" (Examiner's January 2, 2014 Office Action). In response, Appellant elected the non-steroidal glucocorticoid receptor specific antagonist:

> (R)-6-(4-*tert*-Butyl-benzenesulfonyl)-4a-ethoxymethyl-1-(4-fluoro-phenyl)-4,4a,5,6,7,8-hexahydro-1H-1,2,6-triaza-cyclopenta[b]naphthalene, having the following structure:



(Appellant's February 28, 2014 Response 2.)

Appellant's claims 1, 15, and 25 are reproduced below:

> 1. A method for ameliorating the symptoms and/or slowing the rate of disease progression in a patient diagnosed with amyotrophic lateral sclerosis (ALS), the method comprising: administering daily doses of a therapeutically effective amount of a non-steroidal glucocorticoid receptor specific antagonist (GRA) to a subject in need thereof, wherein the glucocorticoid receptor antagonist is administered in a daily

canceled"); Examiner's September 10, 2019 Office Action (Appellants "response filed 7/2/2019 has been received and entered in the application")).

> amount of between about 0.5 mg and about 40 mg per kg of body weight per day, and wherein said GRA specifically antagonizes type II glucocorticoid receptor functions but does not significantly antagonize type I glucocorticoid receptor (mineralocorticoid receptor) functions, with the proviso that the subject not be otherwise in need of treatment with a glucocorticoid receptor antagonist, whereby said symptoms are ameliorated and/or the rate of disease progression is slowed in said ALS patient.

(Appeal Br. 33.)

> 15. The method of claim 1, wherein the glucocorticoid receptor antagonist is an azadecalin or a fused ring azadecalin compound.

(*Id.*)

> 25. The method of claim 1, wherein the binding affinity of the GRA for the type II glucocorticoid receptor is at least 100-fold greater than the binding affinity of the GRA for the type I glucocorticoid receptor (mineralocorticoid receptor).

(*Id.* at 34.)

Due to the species election discussed above, we review Appellant's claimed invention in the context of a non-steroidal glucocorticoid receptor specific antagonist (GRA) that is (R)-6-(4-*tert*-Butyl-benzenesulfonyl)-4a-ethoxymethyl-1-(4-fluoro-phenyl)-4,4a,5,6,7,8-hexahydro-1H-1,2,6-triaza-cyclopenta[b]naphthalene. *See generally Ex parte Ohsaka*, 2 USPQ2d 1460, 1461 (BPAI 1987).

Claims 1, 15, 17–26, and 28–33 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Clark,[3] Carrì,[4] and Sapse.[5]

ISSUE

Does the preponderance of evidence relied upon by Examiner support a conclusion of obviousness?

FACTUAL FINDINGS (FF)

FF 1. Clark discloses that "GR modulators may . . . affect a wide variety of disease states, such as . . . neurodegeneration (e.g. Alzheimer's disease and Parkinson's disease)" (Clark ¶ 66; *see* Ans. 4).

FF 2. Clark "provides methods of treating a disorder or condition through antagonizing a glucocorticoid receptor," wherein "[t]he method includes administering to a subject in need of such treatment, an effective amount of [Clark's disclosed] compound" (Clark ¶ 15).

FF 3. Clark discloses "a novel class of fused ring azadecalin compounds and methods of using the compounds as glucocorticoid receptor [(GR)] modulators" (Clark, Abstract; *see* Ans. 4; *see also* Appellant's February 28, 2014 Response 2 (citing Clark ¶ 365) (Appellant recognizes that Clark expressly discloses Appellant's elected non-steroidal glucocorticoid receptor specific antagonist (GRA), (R)-6-(4-*tert*-Butyl-benzenesulfonyl)-4a-ethoxymethyl-1-(4-fluoro-phenyl)-4,4a,5,6,7,8-hexahydro-1H-1,2,6-triaza-cyclopenta[b]naphthalene)).

[3] Clark et al., WO 2005/087769 A1, published Sept. 22, 2005.
[4] Carrì et al., *Neurodegeneration in amyotrophic lateral sclerosis: the role of oxidative stress and altered homeostatsis of metals*, 61 Brain Research Bulletin 365–374 (2003).
[5] Sapse et al., US 2005/0085464 A1, published Apr. 21, 2005.

FF 4. Clark discloses "pharmaceutical formulations for oral administration of GR modulator is in a daily amount of between about 0.5 to about 20 mg per kilogram of body weight per day" (Clark ¶ 233; *see* Ans. 4).

FF 5. Examiner finds that although Clark discloses the use of a GR modulator to treat neurodegenerative disorders, Clark does not expressly disclose the treatment of "amyotrophic lateral sclerosis (ALS)" (Ans. 5).

FF 6. Carrì discloses that ALS "is one of the most common neurodegenerative disorders" (Carrì, Abstract; *see* Ans. 5).

FF 7. Examiner relies on Sapse to disclose "that tracking and treating increased levels of cortisol could be used to treat or prevent high cortisol diseases such as . . . [ALS], where elevated cortisol is constantly found" (Ans. 5 (citing Sapse ¶ 4) (emphasis omitted)).

ANALYSIS

Based on the combination of Clark, Carrì, and Sapse, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to treat ALS, the most common neurodegenerative disorder, by administering (R)-6-(4-tert-Butyl-benzenesulfonyl)-4a-ethoxymethyl-1-(4-fluoro-phenyl)-4,4a,5,6,7,8-hexahydro-1H-1,2,6-triaza-cyclopenta[b]naphthalene at a dosage of 0.5 to about 20 mg per kilogram of body weight per day (*see generally* Ans. 5–6; *see also* FF 1–6). *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) ("[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness.").

In sum, the combination of Clark, Carrì, and Sapse makes obvious the treatment, i.e. amelioration and/or slowing the rate of disease progression, of a neurodegenerative disorder, such as ALS, in a subject by administering

Appellant's elected non-steroidal glucocorticoid receptor specific antagonist (GRA), to a patient in need of such treatment, in an amount that falls within that required by Appellant's claimed invention (*see* FF 1–6). Because the GRA taught by the prior art relied upon by Examiner is the same GRA elected by Appellant we find no error in Examiner's finding that the prior art GRA: (a) is a fused ring azadecalin compound; (b) will specifically antagonize type II glucocorticoid receptor functions but will not significantly antagonize type I glucocorticoid receptor (mineralcorticoid receptor) functions; and (c) has a binding affinity for the type II glucocorticoid receptor that is at least 100-fold greater than the binding affinity of the GRA for the type I glucocorticoid receptor (mineralocorticoid receptor) (*see, e.g.,* Ans. 8, and 25; *see also* FF 1–6).

Claim 1:

Clark expressly discloses the administration of an effective amount[6] of a compound that *antagonizes a glucocorticoid receptor*, i.e. Appellant's elected GRA, to treat, *inter alia*, a neurodegeneration disorder (see FF 1–4 (emphasis added)). ALS "is one of the most common neurodegenerative disorders" (FF 6). Therefore, we are not persuaded by Appellant's contention that the combination of Clark, Carrì, and Sapse "does ***not*** teach the use of GR **antagonists** to affect neurodegeneration, and makes no suggestion that GR **antagonists** might be used to treat ALS" (Appeal Br. 13 (citing Clark Decl.[7] ¶¶ 7 and 9–11); *see also* Appeal Br. 18 (Appellant

[6] For example, the daily oral administration of between about 0.5 to about 20 mg per kilogram of body weight per day (*see* FF 4).
[7] Declaration of Robin D. Clark, Ph.D., signed Sept. 16, 2015.

contends that "Examiner . . . presented no evidence that one class of drugs, such as non-steroidal GRA's, can be used to effectively treat different neurodegenerative diseases" or that the references cited by Examiner "contradict each other"); Reply Br. 14–15 (Appellant contends that "because [Carrì] suggests that metal-mediated oxidative stress was thought to be one of the main mechanisms in the pathogenesis of ALS, and [Carrì] does not provide any guidance on administering GRAs to treat a symptom of ALS" "a person of ordinary skill in the art reading [Carrì] would not be motivated to treat ALS with the claimed GRA, and would not have a reasonable expectation of success")).

For the foregoing reasons, we are not persuaded by Appellant's contention that "Clark discusses GR 'modulators' yet provides no suggestion or guidance to select GR antagonists; thus, there is no teaching or suggestion in the reference leading one of ordinary skill in the art to modify Clark in order to provide the claimed treatment for ALS" (Appeal Br. 14 (emphasis omitted); *see id.* at 21 (Appellant contends that "Clark does not provide any guidance on what type of GR modulator would be suitable to treat a given neurodegenerative disease, let alone that a GRA would be effective")). For the same reasons, we are not persuaded by Appellant's contention that "[n]one of the cited references provide a 'detailed enabling methodology' for treating ALS with the claimed GRA, and none of the cited references, nor their combination, provide any evidence suggesting that it would be successful, therefore claim 1 is not obvious in view of the cited references" (Appeal Br. 15) (emphasis omitted). In this regard we note that "[o]bviousness does not require absolute predictability of success . . . all that

is required is a reasonable expectation of success," which, on this record, is provided by Clark. *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

For the foregoing reasons, we are not persuaded by Clark's testimony that "in my scientific opinion, a scientist in the field would not have considered the term 'GR modulator' as used in the Clark application[, of which declarant is listed as an inventor,] to include GR antagonists for treating neurodegeneration diseases (Clark Decl. ¶ 11; *see id.* ¶¶ 5–10 and evidence cited therein). For the same reasons, we are not persuaded by Belanoff's testimony that, as the inventor of the subject matter claimed herein, "it is my considered opinion that the combination of Clark and [Carrì] does not suggest that a GR modulator might be used to treat ALS" and "[i]n particular . . . that the combination of Clark and [Carrì] does not suggest that GR modulator (R)-6-(4-tert- Butyl-benzenesulfonyl)-4a-ethoxymethyl-1-(4-fluoro-phenyl)-4,4a,5,6,7,8-hexahydro-1H-1,2,6-triaza-cyclopenta[b]naphthalene might be used to treat ALS" (Belanoff Decl.[8] ¶¶ 3 and 16; *see also id.* ¶¶ 4–15 and evidence cited therein). For the foregoing reasons, we are not persuaded by De Nicola's testimony that "a scientist in the field would not consider the cited references when seeking to treat the symptoms of ALS with a type II GRA" (De Nicola Decl.[9] ¶ 15; *see also id.* ¶¶ 3–14 and evidence cited therein; Appeal Br. 23–26 (citing De Nicola Decl. ¶¶ 7–9) (Appellant relies on De Nicola's testimony to support a contention that "there was no reason to expect that a glucocorticoid antagonist would be effective at treating ALS"); Appeal Br. 17 (quoting De Nicola Decl. ¶ 14) (Appellant relies on De Nicola's testimony to support a

[8] Declaration of Joseph K. Belanoff, M.D., signed Dec. 12, 2016.
[9] Declaration of Alejandro F. De Nicola, signed June 28, 2019.

contention that at the time of Appellant's claimed invention, "there was no reason to select a GRA to treat any neurodegenerative disease, let alone ALS")). For the same reasons, we are not persuaded on Appellant's reliance on Fidler[10] to support a contention "that a scientist in the field would not consider treating ALS with a type II GRA" (Appeal Br. 26; *see also id.* at 27 (citing De Nicola Decl. ¶ 19 (Appellant contends that De Nicola's testimony "that a scientist in the field would not consider treating ALS with a type II GRA [was] based on the Fidler article"); *see also* Appeal Br. 27–29; Reply Br. 11–14).

We acknowledge Belanoff's testimony that Alzheimer's disease (AD) and Parkinson's disease (PD) affect different types of neurons located in different parts of the brain (*see generally* Belanoff Decl.[11] ¶¶ 5–10). We note, however, that Clark discloses that its GR modulators can affect a wide variety of disease states including neurodegeneration, for example Alzheimer's disease and Parkinson's disease (*see* FF 1). Thus, as Belanoff's testimony makes clear, Clark discloses that its GR modulators affect neurodegenerative disorders implicating different types of neuron and/or regions of the brain.

For the foregoing reasons, we are not persuaded by Belanoff's testimony that because each of ALS, AD, and PD involve different a neuron types and brain regions Belanoff would not expect Clark's disclosed treatment "would be likely to help in treating ALS" (*see* Belanoff Decl.

[10] Fidler et al., *Disease progression in a mouse model of amyotrophic lateral sclerosis: the influence of chronic stress and corticosterone*, 25 FASEB J. 4369–4377 (2011).
[11] Declaration of Joseph K. Belanoff, M.D., signed Dec. 12, 2016.

¶¶ 5–10; *see also* Appeal Br. 16–17 and 21 (Appellant contends, based on Belanoff's testimony, that "one of ordinary skill in the art would not have a reasonable expectation that the same treatment would apply to different neurodegenerative diseases")). For the same reasons, we are not persuaded by Appellant's reliance on De Nicola's testimony that "despite being referred to as a neurodegenerative disease, ALS is a disease with distinct etiology and pathogenic mechanisms compared to other neurodegenerative diseases. The cells that are targeted in ALS are motor neurons, whereas the other neurodegenerative diseases target different cells types in the CNS" (Appeal Br. 17 (quoting De Nicola Decl. ¶ 14); *see also* Reply Br. 14 (citing Belanoff Decl. ¶¶ 5–8) (contending that "different neurodegenerative diseases affect different cell types")).

Carrì discloses that ALS is a neurodegenerative disorder (FF 6). Clark discloses the use of Appellant's elected GRA for the treatment of neurodegenerative disorders (FF 1–4). Therefore, we are not persuaded by Appellant's reliance on Petrov[12] to establish that non-GRA compounds were tested in human ALS clinical trials (Appeal Br. 19–20). For the same reasons, we are not persuaded by Appellant's reliance on Cummings[13] or Orayj[14] to establish that "no GRAs are approved for treating other neurodegenerative diseases" (*id.* at 20; *see also id.* at 16 (Appellant contends

[12] Petrov et al., *ALS Clinical Trials Review: 20 Years of Failure. Are we Any Closer to Registering a New Treatment?*, 8 Frontiers in Aging Neuroscience 1–11 (2017).
[13] Cummings et al., *Treatment Combinations for Alzheimer's Disease: Current and Future Pharmacotherapy Options*, 67 Journal of Alzheimer's Disease 779–794 (2019).
[14] Orayj et al., *Patterns and Determinants of Prescribing for Parkingon's Disease: A Systematic Literature Review*, Parkinson's Disease 1–40 (2019).

"that known treatments and clinical trials to treat [Alzheimer's Disease], [Parkinson's Disease] and ALS do not use the same drugs, and instead use unrelated drugs with totally different mechanisms of action")).

As discussed above, Clark discloses "a novel class of fused ring azadecalin compounds[, including Appellant's elected GRA,] and methods of using the compounds as glucocorticoid receptor modulators" to treat neurodegenerative disorders of which ALS "is one of the most common" (FF 1–4 and 6). Therefore, we are not persuaded by Appellant's contention that its claim 1 is "not obvious because one of ordinary skill in the art would not have been motivated to use a type II GRA to treat ALS based on the combination of cited references" (Appeal Br. 21). We are also not persuaded by Appellant's intimation that it would require undue experimentation to select Appellant's elected GRA, which is expressly exemplified by Clark as a species within its disclosed novel class of fused ring azadecalin compounds (*see id*. (Appellant contends that "the skilled artisan would have to test a very large number of compounds that are considered GR modulators to arrive at the instant claims"); *cf.* FF 1–4).

For the foregoing reasons, we are not persuaded by Appellant's contentions regarding cortisol (*see e.g.,* Appeal Br. 9, 12, 14, 15, 18, 21, and 24; *see also* Reply Br. 3–6 and 15). For the same reasons, we are not persuaded by Appellant's contentions regarding the GRA disclosed by Sapse (*see e.g.,* Appeal Br. 24 (citing De Nicola Decl. ¶ 6)).

Weighing the totality of evidence on this record, we find that Clark's disclosure of treating neurodegenerative disorders, of which ALS is one of the most common, with an effective amount of a glucocorticoid receptor antagonist, including Appellant's elected GRA outweighs Appellant's

contentions that the method of Appellant's claim 1 "was unexpected in view of [Appellant's asserted] substantial skepticism in the art at the time the instant application was filed" (Appeal Br. 28 (citing De Nicola Decl. and Hunt Decl.[15]); *see also* Reply Br. 9).

Claim 15:

As discussed above, the combination of Clark, Carrì, and Sapse makes obvious the treatment, i.e. amelioration and/or slowing the rate of disease progression, of a neurodegenerative disorder, such as ALS, in a subject by administering *Appellant's elected non-steroidal glucocorticoid receptor specific antagonist (GRA)*, to a patient in need of such treatment, in an amount that falls within that required by Appellant's claimed invention (*see* FF 1–6). Therefore, we are not persuaded by Appellant's contention that "none of the cited references, alone or in combination, suggest that [Appellant's] elected species of GR ***antagonists*** can be used to treat ALS" (Appeal Br. 30).

Claim 25:

As discussed above, because the GRA taught by the combination of Clark, Carrì, and Sapse is the same GRA elected by Appellant, we find no error in Examiner's finding that the prior art GRA, *inter alia*, will specifically antagonize type II glucocorticoid receptor functions but will not significantly antagonize type I glucocorticoid receptor (mineralcorticoid receptor) functions and have a binding affinity for the type II glucocorticoid

[15] Declaration of Hazel Hunt, Ph.D., signed July 13, 2016.

receptor that is at least 100-fold greater than the binding affinity of the GRA for the type I glucocorticoid receptor (mineralocorticoid receptor) (*see, e.g.,* Ans. 8, and 25; *see also* FF 1–6). Therefore, we are not persuaded by Appellant's contention that Sapse's disclosure of "RU 486, which is a steroid that binds to the progesterone and glucocorticoid receptors . . . is not relevant to the instant claims, because it does not specifically antagonize type II glucocorticoid receptor functions" (Appeal Br. 30).

CONCLUSION

The preponderance of evidence relied upon by Examiner supports a conclusion of obviousness. The rejection of claims 1, 15, and 25 under 35 U.S.C. § 103(a) as unpatentable over the combination of Clark, Carrì, and Sapse is affirmed. Claims 17–24 are not separately argued and fall with claim 1. Claims 26 and 28–33 are not separately argued and fall with claim 25.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 15, 17–26, 28–33	103(a)	Clark, Carrì, Sapse	1, 15, 17–26, 28–33	

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED