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Sheridan Ross PC
1560 Broadway
Suite 1200
Denver, CO 80202

EXAMINER	
BERRIOS, JENNIFER A	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DAVID BAR-OR

Appeal 2019-005422
Application[1] 14/353,833
Technology Center 1600

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of reducing the severity of symptoms of allergic rhinitis, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

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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 AMPIO PHARMACEUTICALS, INC. (Appeal Br. 3.)

STATEMENT OF THE CASE

"Rhinitis is caused by chronic or acute inflammation of the mucous membranes of the nose due to viruses, bacteria or irritants." (Spec. 1.) "Allergic rhinitis is a proinflammatory immune response to outdoor or indoor allergens, such as dust or pollen." (*Id.*) "The inflammation results in the generation of excessive amounts of mucous, commonly producing a runny nose, nasal congestion and post-nasal drip." (*Id.*) Appellant's invention is a method to reduce the severity of symptoms of allergic rhinitis.

Claims 1, 2, 4–7, and 9–13 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method of reducing the severity of the symptoms of allergic rhinitis comprising administering an effective amount of a pharmaceutical composition comprising a diketopiperazine with amino acid side chains of aspartic acid and alanine (DA-DKP), to an animal in need thereof, wherein the DA-DKP is in a composition prepared by removing albumin from a solution of a human serum albumin composition, wherein the effective amount of the DA-DKP in the composition is from about 100 μg to about 3000 μg per day.

(Appeal Br. 19.)

The prior art relied upon by the Examiner is:

Name	Reference	Date
Alkeret al.	US 5,358,953	Oct. 25, 1994
Bar-Or et al.	US 6,555,543 B2	Apr. 29, 2003
Ivanova et al.	US 2004/0048795 A1	Mar. 11, 2004
Bonner	US 2009/0038416 A1	Feb. 12, 2009
D. H. Albert et al., *ABT-491, a highly potent and selective PAF antagonist, inhibits nasal vascular permeability associated with experimental allergic rhinitis in Brown Norway rats*, 46(Suppl. 2) Inflammation Res. S133–34 (1997)		
E. O. Meltzer, *Efficacy and Patient Satisfaction with Cromolyn Sodium Nasal Solution in the Treatment of Seasonal Allergic Rhinitis: A Placebo-Controlled Study*, 24(6) Clin. Therap. 942–52 (2002)		
D. Bar-Or et al., *Commercial human albumin preparations for clinical use are immunosuppressive in vitro*, 34(6) Crit. Care Med. 1707–12 (2006) (Bar-Or 2006)		

The following grounds of rejection by the Examiner are before us on review:

Claims 1, 2, 4, and 9–13 under 35 U.S.C. § 103(a) as unpatentable over Bar-Or, Albert, and Alker.

Claims 5–7 under 35 U.S.C. § 103(a) as unpatentable over Bar-Or, Albert, Alker, Bonner, and Meltzer.

Claims 1, 2, 4, and 9–13 under 35 U.S.C. § 103(a) as unpatentable over Bar-Or, Albert, Bar-Or 2006, Ivanova, and Alker.

Claims 5–7 under 35 U.S.C. § 103(a) as unpatentable over Bar-Or, Albert, Bar-Or 2006, Ivanova, Alker, Bonner, and Meltzer.

DISCUSSION

Non-Obviousness Bar-Or, Albert, Alker

The Examiner finds that Bar-Or discloses a method of inhibiting the effects of platelet activating factor (PAF) with DA-DKP where the suitable daily dose of DA-DKP "will be the amount of the compound which is the lowest dose effective to produce a therapeutic effect" and "will be determined by an attending physician or veterinarian within the scope of sound medical judgement." (Final Action 3–4.) The Examiner further finds that Bar-Or teaches that a disease "mediated by PAF (particularly inflammation) can be treated" (*id.* at 3) by administration of the compound "until an acceptable response is achieved" (*id.* at 4). The Examiner explains that Bar-Or's method is based "on the discovery that [DA-DKP] inhibits PAF activity" which "inhibition appears to be due to the binding of DA-DKP to both PAF and PAF receptors." (*Id.* at 3.)

The Examiner recognizes that Bar-Or does not teach using DA-DKP to treat allergic rhinitis, which is required by all the claims. (*Id.* at 4.) However, the Examiner finds that such would have been obvious from the combined teachings of Bar-Or, Albert, and Alker. (*Id.*; Ans. 18.) In particular, the Examiner finds that Albert teaches that "PAF is perhaps the most potent for inducing vascular permeability, a response that may contribute to rhinorrhea formation" and "[t]he role of PAF in allergic rhinitis has also been supported by studies reported with several PAF antagonists in animal models of the disease." (*Id.* at 4–5.) In addition, Albert teaches that "ABT-491 exhibited potent [antagonist] activity" against nasal vascular permeability in an animal model that resulted from an acute inflammatory response after administration of PAF. (*Id.* at 5; Ans. 18.) The Examiner

further notes that "[w]hile Albert specifically teaches the use of ABT-491, Albert makes the conclusion that PAF plays an important role in antigen-induced increased nasal vascular permeability in the rat and supports the potential clinical utility of [any] PAF antagonist for the treatment of this disease." (Ans. 18; *see also* Final Action 5 ("Albert concludes that a PAF antagonist has the potential for treatment of [allergic rhinitis].").)

The Examiner concludes that because DA-DKP is a potent PAF antagonist, it would have been expected by one of ordinary skill in the art to function in the same manner as ABT-491 in treating rhinitis "absent evidence to the contrary" and one of ordinary skill in the art would have been motivated to use the compositions of Bar-Or for the treatment of allergic rhinitis in a person in need. (*Id.*; Final Action 5.) In further support of this conclusion, the Examiner notes that Alker teaches imidazopyridine is a PAF antagonist that has "a structure very different from ABT-491 and DA-DKP, however, these structurally different compounds are capable of treating allergic rhinitis." (Ans. 18; *see also* Final Action 7–8 (describing the teachings of Alker).)

Regarding the claimed dosage amount, the Examiner notes that Alker teaches using the imidazopyridine PAF/H1 antagonists at dose levels of from 0.1-50 mg by intranasal administration and that a physician will determine the actual dose that is most suitable for an individual patient. (Final Action 7–8.) The Examiner concludes that "one of skill in the art would recognize 0.1-50mg of DA-DKP to be starting point for optimization to determine the ideal quantity of DA-DKP to be administered, as both Alker and Bar-Or teaches that the amount of drug used to achieve a therapeutic

effect depends on the individual patient and will vary with weight, age and response of the patient." (*Id.*)

Finally, regarding the claimed manner by which the DA-DKP is obtained, the Examiner explains that in light of the fact that Bar-Or appears to teach the same claimed compound, even though it may be produced by a different process, "the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product." (Final Action 5–7.)

We conclude that the record does not support the Examiner's conclusion of obviousness as to the motivation and reasonable expectation of success of treating allergic rhinitis with DA-DKP.

Appellant submitted Abu-Zidan[2] in support of the unreasonableness of the Examiner's conclusion that just because two compounds have been determined to be a PAF antagonist is not sufficient for one of ordinary skill in the art to draw a conclusion that they would reasonably be expected to treat the same inflammatory condition. The Examiner discounts any relevance of this reference because the reference is concerned with PAF antagonists in ischemic shock, which the Examiner indicates "does not appear to be related to allergic rhinitis and inflammation and the prior art shows that PAF antagonists, specifically DA-DKP and ABT-149, act against inflammation mediated by PAF." (Ans. 19.) We disagree with the Examiner that Abu-Zidan is not relevant evidence contradicting the Examiner's reasonable expectation assertion.

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[2] F. M. Abu-Zidan et al., *Lexipafant (BB-882): A Potent New Platelet-Activating Factor Receptor Antagonist*, 15(3) Cardiovascular Drug Reviews 232–43 (1997).

Abu-Zidan teaches that there are "different PAF receptor subtypes in the same animal" and that "different tissues respond differently to PAF" and notes that there may be "subtype-selectivity of different PAF receptor antagonists." (Abu-Zidan 238.) Abu-Zidan also indicates that different PAF antagonist compounds, particularly those that have different structures, may give rise to different effects due to blocking different PAF receptors. (*Id.*) Indeed, Abu-Zidan observed a difference in effect of different PAF antagonist compounds (lexipafant and WEB 2086) in models of sepsis, which Abu-Zidan indicates is a condition characterized by systemic inflammation. (*Id.* at 232, 235–38.)

We agree with Appellant that Abu-Zidan supports the conclusion that one of ordinary skill in the art would not have had a reasonable expectation that DA-DKP would treat the same condition as ABT-491 just because both ABT-491 and DA-DKP have PAF antagonist activity. (Appeal Br. 12–13.) We note that the PAF antagonist activity Bar-Or studied is with respect to IL-8 secretion in bronchial epithelial cells. (Bar-Or 13:30–67.) The PAF antagonist activity studied in Albert was antigen-induced nasal vascular-permeability. (*See, e.g.*, Albert S133 (Materials and methods: noting perfusion of the nasal mucosa) and *id.* at S134 (Results and discussion: noting potent activity as an antagonist of PAF provoked increased nasal vascular permeability).) In other words, different inflammatory responses were analyzed and in different tissues.

Furthermore, as Appellant explains, ABT-491 and DA-DKP have significantly different structures (Appeal Br. 11), which the Examiner acknowledges (Ans. 19).

Albert indicates that its studies, which were directed at observing a reduction in increased vascular permeability provoked by PAF, "support the potential clinical utility of a PAF antagonist for the treatment" of allergic rhinitis. (Albert S134.) Albert itself suggests that it is not simply the fact of any PAF antagonist activity that is important to suggest potential utility, but rather PAF antagonist activity that results in reducing increased vascular permeability. The Examiner has not established that DA-DKP has PAF antagonist activity that results in reducing increased vascular permeability.

Abu-Zidan provides a reason to doubt that one of ordinary skill in the art would have considered Albert to suggest that any PAF antagonist would reasonably be expected to work just because it is a PAF antagonist. That is because as noted above, Abu-Zidan teaches that it was known that different compounds with PAF antagonist activity may act on different receptor subtypes. The Examiner does not assert that it was known that DA-DKP and ABT-491 act on the same PAF receptor subtype. Moreover, the studies conducted in Bar-Or and Albert were on different tissues and involved studying different activity. Given that DA-DKP and ABT-491 have a significantly different structure, we find that it is not reasonable to conclude in the absence of the foregoing evidence that both compounds will act on the same PAF receptor in the same tissue.

The Examiner contends that because Alker teaches a different PAF antagonist compound than Albert that also is taught to have utility in treating allergic rhinitis, that the difference in structure between ABT-491 and DA-DKP would not counsel against a reasonable expectation of success. (Ans. 19.) We disagree. That is because the bulky multiple ring structure of the Alker compound is much closer to the bulky multiple ring structure of ABT-

491 described in Albert than it is to the single ring structure of DA-DKP. (*Compare* Alker 2 *with* Appeal Br. 11.)

For the foregoing reasons, we reverse the Examiner's rejection of claims 1, 2, 4, and 9–13 under 35 U.S.C. § 103(a) as unpatentable over Bar-Or, Albert, and Alker.

The Examiner's reliance on Bonner and Meltzer in rejecting claims 5–7 does not address the deficiencies of Bar-Or, Albert, and Alker just discussed. Consequently, we also reverse the Examiner's rejection of claims 5–7 under 35 U.S.C. § 103(a) as unpatentable over Bar-Or, Albert, Alker, Bonner, and Meltzer.

Non-Obviousness Bar-Or, Albert, Bar-Or 2006, Ivanova, Alker

The Examiner relies on Bar-Or, Albert, and Alker for the teachings discussed above. (Final Action 12–14.) The Examiner relies on Bar-Or 2006 for its teaching of DA-DKP being extracted from HSA (human serum albumin) commercial preparations, and that the compound is "partially responsible for the immunosuppressive effects of H[SA] on activated PBMCs and T-lymphocytes" and that "H[SA] preparations[, all of which included DA-DKP,] significantly inhibited the in vitro production of interferon-γ and tumor necrosis factor by activated PMBCs." (*Id.* at 14–15.)

The Examiner notes that Ivanova teaches that "PAF, along with interferon-γ and tumor necrosis factor are proinflammatory cytokines." (*Id.* at 15.) According to the Examiner:

> As DA-DKP was shown to have inhibitory effects against the proinflammatory cytokines interferon-γ and tumor necrosis factor, one of skill in the art would have reasonably expected DA-DKP prepared by the method of [Bar-Or 2006] to also be effective against PAF, which is shown to be a functionally

> equivalent compound (proinflammatory cytokine) to both interferon-γ and tumor necrosis factor.

(*Id.*) The Examiner concludes that "[t]herefore, it would have been prima facie obvious to use the DA-DKP prepared by the method of Bar-Or NPL as the DA-DKP used in the method of treating rhinitis made obvious [b]y Bar-Or and Alberta." *Id.*

The Examiner's reliance on Bar-Or 2006 and Ivanova does not cure the deficiencies discussed above. The fact that interferon-γ, tumor necrosis factor, and PAF are all proinflammatory cytokines does not address or suggest that DA-DKP would be expected to have PAF antagonist activity that results in reducing increased vascular permeability. Consequently, we also do not affirm the Examiner's rejection of claims 1, 2, 4, and 9–13 under 35 U.S.C. § 103(a) as unpatentable over Bar-Or, Albert, Bar-Or 2006, Ivanova, and Alker, or of claims 5–7 under 35 U.S.C. § 103(a) as unpatentable over Bar-Or, Albert, Bar-Or 2006, Ivanova, Alker, Bonner, and Meltzer.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 2, 4, 9–13	103	Bar-Or, Albert, Alker		1, 2, 4, 9–13
5–7	103	Bar-Or, Albert, Alker, Bonner, Meltzer		5–7
1, 2, 4, 9–13	103	Bar-Or, Albert, Bar-Or 2006, Ivanova, Alker		1, 2, 4, 9–13
5–7	103	Bar-Or, Albert, Bar-Or 2006, Ivanova, Alker, Bonner, Meltzer		5–7
Overall Outcome				1, 2, 4–7, 9–13

REVERSED