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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SOLOMON H. SNYDER, MOATAZ M. GADALLA,
NANDURI R. PRABHAKAR, GREGORY STEIN, and GARY PACE

Appeal 2018-006561
Application 13/640,711
Technology Center 1600

Before DEMETRA J. MILLS, FRANCISCO C. PRATS, and
MICHAEL A. VALEK, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant¹ appeals from the Examiner's decision to reject claims 1, 2, 5, 6, 17, 19, 27, 28, and 31. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

NATURE OF INVENTION

The invention relates to treatments for central sleep apnea. According to the Specification

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 The University of Chicago and Johns Hopkins University. Appeal Br. 1.

The carotid body comprises peripheral chemoreceptors that are linked to the chemoreceptors found in the brainstem. The carotid body controls ventilation by monitoring oxygen and/or carbon dioxide levels in arterial blood. Accordingly, in some embodiments, provided herein are methods for treatment of Central Sleep Apnea comprising administration of agents that modulate the activity of the carotid body (e.g., CSE [cystathionine γ -lyase Enzyme] inhibitors or partial inhibitors, HO-2 inhibitors or partial inhibitors, H₂S donors, CO donors or any other agents described herein) to individuals in need thereof.

Spec. ¶ 91. “In rodent models[,] chronic intermittent hypoxia enhances carotid body responses to hypoxia, and the ensuing chemo-reflex mediates increases in sympathetic nerve activity resulting in elevated blood pressure.”

Spec. ¶ 89. In one example in the Specification, hypoxia increased H₂S levels in a stimulus-dependent manner. The magnitude of hypoxia-evoked H₂S production was comparable in rat and mouse. In DL-propargylglycine (PAG) treated rats, basal H₂S levels were reduced by 55% (vehicle= 266 ± 61 vs. PAG = 147 ± 50 nmol/h/mg protein; p < 0.05) and hypoxia-evoked H₂S generation was nearly absent in carotid bodies. Spec. ¶ 165.

STATEMENT OF CASE

The following claim is representative.

1. A method of treating or reducing incidence of a central sleep apnea syndrome (CSAS) disorder in an individual diagnosed with CSAS comprising administering a therapeutically effective amount of DL-propargylglycine (PAG), beta cyano L-alanine (BCA), or combinations thereof, wherein the individual is not suffering from anatomically compromised airway patency of an obesity individual.

Cited References

Zhang et al., “*Serum level of endogenous hydrogen sulfide in patients with obstructive sleep apnea hypopnea syndrome*”; 2009; Zhongguo Shiyong Neike Zazhi; 29(11): 1049–1050; SciFinder abstract; Accession Number: 2009:1621936.

Olson et al., “*Hypoxic pulmonary vasodilation: a paradigm shift with a hydrogen sulfide mechanism*”; Am. J. Physiol. Regul. Integ. Comp. Physiol.; 2010; 298; R51–R60.

Sun et al., “*Structural Basis for the Inhibition Mechanism of Human Cystathionine γ -Lyase, an Enzyme Responsible for the Production of H_2S* ”; 2009; The Journal of Biological Chemistry; 284(5): 3076–3085).

Livertox, “*Carbonic Anhydrase Inhibitor Diuretics*”; <https://livertox.nlm.nih.gov/CarbonicAnhydraseInhibitorDiuretics.htm>; accessed 10/19/2016).

Shakrokh Javaheri, “*Acetazolamide Improves Central Sleep Apnea in Heart Failure*”; 2006; American Journal of Respiratory and Critical Care Medicine; 173(2):234–237).

Cho et al., “*Propargylglycine infusion effects on tissue glutathione levels, plasma amino acid concentrations and tissue morphology in parenterally-fed growing rats*”; 1991; The Journal of nutrition; 121(6): 785–94; SciFinder abstract; Accession No. 1991237445).

Grounds of Rejection

1. Claims 1, 2, 5, 6, 27, 28, and 31 are rejected under pre-AIA 35 U.S.C. §103(a) as being unpatentable over Zhang, Olson, and Sun.
2. Claim 17 is rejected under pre-AIA 35 U.S.C. §103(a) as being unpatentable over Zhang, Olson, Sun, Javaheri, and Livertox.

3. Claim 19 is rejected under pre-AIA 35 U.S.C. §103(a) as being unpatentable over Zhang, Olson, Sun, and Cho.

FINDINGS OF FACT

The Examiner's findings of fact are set forth in the Answer at pages 2–20.

PRINCIPLES OF LAW

In making our determination, we apply the preponderance of the evidence standard. *See, e.g., Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office).

Under § 103, “there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). “The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant’s disclosure.” *In re Dow Chemical Co.*, 837 F.2d 469, 473, (Fed. Cir. 1988) (citations omitted). “[P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.” *In re Kotzab*, 217 F.3d 1365, 1371, (Fed. Cir. 2000).

“The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless

the prior art suggested the desirability of the modification.” *See, e.g., In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992); *see also, in accord, Cordis Corp. v. Medtronic Ave, Inc.*, 511 F.3d 1157, 1172 (Fed. Cir. 2008) (jury instruction requiring suggestion of desirability of modifying prior held not inconsistent with flexible TSM test articulated in *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007)).

Where a prior art reference provides only, “an invitation to scientists to explore a new technology that seems a promising field of experimentation,” and “gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it,” it “may make an approach ‘obvious to try’ but it does not make the invention obvious.” *Ex parte Obukowicz*, 27 USPQ2d 1063, 1065 (Bd. Pat. App. Int. 1992). (“An “obvious to try rationale” may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. We do not find that the invitation for further experimentation ... provides a reasonable expectation of success.”)

Obviousness Rejection

There is an election of species in this case. Appellant elected:

- (1) Carotid body modulator - DL-propargylglycine (PAG), also known as 2-amino-4-pentynoic acid, CAS No. 64165-64-6,
- (2) Sleep-related disorder - central sleep apnea; and
- (3) Second Agent - carbonic anhydrase inhibitors. Final Act. 2.

When the examiner has required the applicant to elect single chemical species for examination, the issue on appeal is the patentability of the single

elected species. It is appropriate to limit discussion to that single issue and take no position respecting the patentability of the broader generic claims, including the remaining, non-elected species. *See, Ex parte Ohsaka*, 2 USPQ2d 1460 (Bd. Pat. App. Int. 1987). We limit our decision to the elected species.

The Examiner finds that,

Zhang establishes that patients with OSAHS (a type of sleep apnea syndrome, as evidenced by claims 2, 28, which recite OSA) have significantly elevated levels of H₂S (for non-hypertensive patients with OSAHS) in collected serum, relative to healthy controls. The skilled artisan would immediately envisage that therapies that reduce levels of H₂S would be suitable, with an expectation for benefiting these patients. Zhang does not teach applicant elected PAG being administered to these patients, and does not teach the related, elected disorder of central sleep apnea.

Final Act. 6. The Examiner relies on Olson as teaching that “[t]he mechanical effects of H₂S were identical to those produced by hypoxia in cow and sea lion pulmonary arteries.” Ans. 9.

The Examiner finds that Olson implies that this process

plays a role in sleep apnea [and] is suggestive that reducing H₂S levels may play a therapeutic benefit in sleep apnea. Such reduction may be accomplished by interfering with one of the enzymes that play a role in producing H₂S, including CSE. When taken together with Zhang, which recognizes elevated H₂S levels in OSAHS, the skilled artisan would have had a reasonable expectation of a therapeutic benefit in sleep apnea by interfering with activity of CSE in patients with sleep apnea (e.g., with central sleep apnea, or obstructive sleep apnea discussed by Zhang).

Final Act. 12–13. According to the Examiner, Sun establishes that the

elected DL-propargylglycine (PAG) inhibits the activity of CSE [cystathione γ -lyase], and alleviates symptoms of diseases associated with H₂S. Thus, PAG would have been an obvious compound to achieve the reduction of CSE activity, suggested by Olsen and obvious over Zhang.

Final Act. 13.

Appellant contends that

Zhang does not teach this benefit and actually provides evidence for the opposite and thus, could be considered to teach away from the claimed invention. Zhang teaches that the level of H₂S is independent of whether or not the patient has OSAHS, since patients with OSAHS can have either an elevated or reduced level of H₂S compared to healthy control. Therefore, one skilled in the art would be led to believe that a reduction in H₂S levels would **not** reduce or treat OSAHS, since Zhang demonstrates that patients with lower than normal H₂S levels still have OSAHS. Last, Zhang does not teach treatment of OSAHS or any CSAS disorder, the latter of which is required by the current claims.

App. Br. 2–3. Appellant further argues that the cited secondary references do not cure the deficiencies of Zhang. App. Br. 3.

ANALYSIS

We do not find that the Examiner has established a prima facie case of obviousness on the evidence before us.

To summarize, Zhang teaches that some patients with sleep apnea have elevated H₂S levels and some have reduced H₂S levels. Zhang, Abstract.

Olson mentions that hypoxic vasodilation (HVD) can be a benefit for elephant seals during routine dives and sleep apnea. Olson R58, right column. Olson found that their study

demonstrates the evolutionary plasticity of fundamental vascular responses that enables them to fit the needs of the organism. ... The disparate responses to hypoxia in cow and sea lion pulmonary arteries provide a unique model system with which to dissect vascular O₂-sensing and signal transduction mechanism(s). This allowed us to provide additional evidence that O₂-dependent H₂S metabolism is involved in vascular O₂ sensing.

Id. at R55, right column. Thus, Olson discussed O₂ sensing, H₂S, and hypoxia in general, but did not model or study differing types of sleep apnea associated with elevated H₂S levels, much less do so in humans. Sun found that, “[i]mpairment of the formation or action of hydrogen sulfide (H₂S), an endogenous gasotransmitter, is associated with various diseases, such as hypertension, diabetes mellitus, septic and hemorrhagic shock, and pancreatitis.” Sun, 3076. Sun found that, “Cystathionine β-synthase and cystathionine γ-lyase (CSE) are two pyridoxal-5'-phosphate (PLP)-dependent enzymes largely responsible for the production of H₂S in mammals [and] inhibition of CSE by DL-propargylglycine (PAG) has been shown to alleviate disease symptoms.” *Id.* Sun does not draw any conclusions or show any associations between cystathionine enzymes and any sleep apnea disorders.

The Examiner concluded from this evidence that

it would have been obvious to one of ordinary skill in the art at the time of the instant invention to administer Applicant elected PAG to [the] Applicant elected patient population, i.e., those with central sleep apnea, or alternatively, to administer PAG to those with obstructive sleep apnea (the Zhang patients), rendering obvious the methods of the instant claims. The motivation would have been to reduce the levels of H₂S, with the objective of benefitting the apnea patients.

Final Act. 13.

We are not persuaded by the Examiner's rationale and conclusion based on the combined cited references. At best, the cited references invite one of ordinary skill in the art to further experiment regarding a possible association between sleep apnea and H₂S levels. No clear conclusion can be drawn from the Zhang reference with respect to H₂S levels and sleep apnea because Zhang teaches that some patients with sleep apnea have elevated H₂S levels and some have reduced H₂S levels. *See* Zhang, Abstract (reporting that the "H₂S level of patients with [obstructive sleep apnea hyponea syndrome] complicated with hypertension was lower than that of healthy controls"). Sun does not draw any association between cystathione enzymes, H₂S levels and sleep apnea. Olson provides no further assistance in overcoming the deficiencies of Zhang and Sun. Olson showed a role for H₂S metabolism in O₂ sensing evidencing that hypoxia consistently contracted cow CPA (conductance pulmonary arteries). Olson R53, right column. However, the response of sea lion CPA to hypoxia was variable: some vessels were relaxed whereas others contracted. *Id.* Thus, like the other references, Olson does not demonstrate any particular correlation between sleep apnea, or related biological mechanisms, and H₂S levels.

Accordingly, we find that the Examiner has failed to show that the combination of the cited references provides a reasonable expectation of success in treating central sleep apnea by administering PAG to lower H₂S levels. Put another way, we find that at most the cited references invite further experimentation concerning a possible relationship between H₂S metabolism and sleep apnea, they do not evidence that one of ordinary skill in the art would have understood administration of PAG to provide a

predictable solution to the problem of central sleep apnea nor do they evidence a reasonable expectation of success in treating central sleep apnea by lowering H₂S levels. For these reasons, the preponderance of evidence does not support Rejection 1.

Rejections 2 and 3 rely on the same primary combination of references and rationale, and are reversed for the same reasons.

CONCLUSION OF LAW

The cited references do not support the Examiner's obviousness rejections 1–3, which are reversed with respect to the elected species.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 2, 5, 6, 27, 28, 31	103	Zhang, Olson, Sun		1, 2, 5, 6, 27, 28, 31
17	103	Zhang, Olson, Sun, Javaheri, Livertox		17
19	103	Zhang, Olson, Sun, Cho		19
Overall Outcome				1, 2, 5,6, 17, 19, 27, 28, 31

REVERSED