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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte BERNHARD FISCHER and RUDOLF LUCAS

Appeal 2017-007135
Application 14/201,119
Technology Center 1600

Before RICHARD M. LEBOVITZ, JEFFREY N. FREDMAN, and MICHAEL J. FITZPATRICK, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134 involving claims to a method for the prevention of edema in a patient suffering acute respiratory distress syndrome by treating with cyclized peptide. The Examiner rejected the claims as anticipated. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] Appellants identify the Real Parties in Interest as Apeptico Forschung und Entwicklung GMBH (*see* App. Br. 2).

[2] We have considered and herein refer to the Specification of June 16, 2014 ("Spec."); Final Office Action of May 9, 2016 ("Final Action"); Appeal Brief of Nov. 4, 2016 ("App. Br."); Examiner's Answer of Feb. 7, 2017 ("Answer"); and Reply Brief of Apr. 6, 2017 ("Reply Br.").

Statement of the Case

Background

"Epithelial cells form single- or multi-layer cell layers, which cover all inner and outer body surfaces of the human and animal organs" (Spec. ¶ 4). "An injury of the endothelium and the epithelium may cause a so-called hyperpermeability, i.e. an uncontrolled passage of liquid from blood vessels into vital organs and tissues" "and thus seriously damage the functionality of the organs" (*id.* ¶ 6–7). "Hyperpermeability of lung tissues is an essential component of various diseases of the lungs, e.g. acute lung injury, acute respiratory distress syndrome (ARDS), pneumonia" (*id.* ¶ 15).

The Claims

Claims 1, 6, and 13 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method for the prevention of edema in a patient suffering acute respiratory distress syndrome (ARDS) by prevention of hyper-permeability, based on injuries of the endothelium and epithelium layers, comprising the steps of:
>
> identifying the patient with (ARDS) prior to the onset of edema; and
>
> providing the patient with an amount of a peptide consisting of the amino acid sequence CGQRETPEGAEAKPWYC (SEQ ID NO: 1) and that is cyclized via the C residues sufficient to prevent the entry of fluid via the endothelium of the capillaries into the epithelium of the lung at the alveoli to reduce an amount of fluid that enters a lung of the patient before edema occurs within the lung of the patient, by increasing the expression of epithelial sodium channel and inhibiting the activation of Protein Kinase C in the endothelium of the capillaries.

The Rejection[3]

The Examiner has rejected claims 1, 6, and 13 under 35 U.S.C. § 102(b) as anticipated by Lucas[4] (Final Act. 3–6).

The Examiner finds Lucas teaches "the circularized peptide CGQRETPEGAEAKPWYC" "containing a disulfide between cysteines" "for the treatment of edema . . . including ARDS" (Final Act. 4). The Examiner finds Lucas teaches

> patients with ARDS have dramatically decreased edema resorption capacity (see e.g. Col. 21 lines 52–55). Further, the model of lung reperfusion injury results in edema, and is a model of ARDS (see e.g. Example 4). Thus, the patients being treated in [Lucas] already have been identified as having ARDS prior to the onset of edema.

(*Id.*).

The Examiner finds the functional recitations in claim 1 of inhibition of activation of protein kinase C and increase in epithelial sodium channel expression are inherent in the administration of the peptide (*see id.* at 5). The Examiner finds overlapping dosage amounts between the Specification and Lucas, and therefore finds administration of the same dosage "must achieve the same result during treatment of edema in a patient suffering from ARDS" (*id.* at 6).

The issue with respect to this rejection is: Does a preponderance of the evidence of record support the Examiner's conclusion that Lucas teaches "prevention of edema" using the claimed peptide as required by claim 1?

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[3] The Examiner withdrew rejections under 35 U.S.C. § 112, first, second, and fourth paragraphs and under 35 U.S.C. § 103(a) (*see* Ans. 5–6).
[4] Lucas et al., US 7,258,861 B2, issued Aug. 21, 2007.

Findings of Fact ("FF")

1. Lucas teaches "the endothelium plays an essential role in regulating the dynamic interaction between pulmonary vasodilatation and vasoconstriction and is a major target during ischemia/reperfusion and acute respiratory distress syndrome (ARDS)-related lung injury . . . there is an urgent need to efficiently prevent or treat pulmonary edema" (Lucas 1:35–43).

2. Lucas teaches "patients with ARDS or acute lung injury also have a dramatically decreased edema resorption capacity, correlating with morbidity and higher mortality" (Lucas 21:52–54).

3. Lucas teaches the "terms 'a pharmaceutical composition for treating oedema' relates to any composition comprising a peptide as defined above which prevents, ameliorates or cures oedema, in particular pulmonary oedema" (Lucas 6:7–10).

4. Lucas teaches "the present invention aims at providing non-toxic peptides derived from TNF which can be used to prevent or treat oedema" (Lucas 2:66 to 3:1)

5. Lucas, teaches, in Example 4, a "Rat Model of Lung Reperfusion Injury (Warm Ischemia and Reperfusion): a Model of Acute Respiratory Distress Syndrome (ARDS)" in which

> rats (200-250 g) undergo clamping of the left pulmonary artery, pulmonary vein and main bronchus for 36 minutes of warm ischemia. After reperfusion of the left lung, the right lung is occluded to assess the function of the left lung for 90 minutes. The peptide is given at 3 minutes after reperfusion by either instillation or intravenous injection via the subclavian vein.

(Lucas 15:1–15).

6. Lucas teaches, in Example 4, that the

> cyclic hum Ltip peptide: CGQRETPEGAEAKPWYC (SEQ ID NO 4; with a disulfide bond between Cys at position 1 and position 17) treated animals (and this over a broad dosage range, extending from 500 µg/kg to 5 µg/kg, have significantly much better pO2 levels and lower pCO2 levels (data not shown) and are less suffering from fluid overload.

(Lucas 16:19–25).

7. Lucas teaches the drug "is given at a dose between 1 µg/kg and 10 mg/kg" (Lucas 6:35–36).

8. The Specification teaches the "drug is administered such that the peptide of the present invention is administered at a dose of between 1 µg/kg and 10 µg/kg, more preferably between 10 µg/kg and 5 mg/kg" (Spec. ¶ 33).

Principles of Law

The Examiner bears the initial burden of establishing a prima facie case of anticipation. *In re King*, 801 F.2d 1324, 1326–27 (Fed. Cir. 1986). Anticipation under 35 U.S.C. § 102 requires that "'each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.'" *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

Analysis

We adopt the Examiner's findings of fact and conclusions of law (see Final Act. 3–6; FF 1–8) and agree that Lucas anticipates the claims. We address Appellants' arguments below.

Appellants contend the "claims are directed to a method that prevents the occurrence of edema within the lung of an ARDS patient before any edema occurs" (App. Br. 9). Appellants contend Lucas "provides a false

definition for the expression 'a pharmaceutical composition for treating edema' because the meaning of the term 'treatment' does not correctly encompass the meaning of the term 'prevention'" (*id.* 10). Appellants contend "[b]ecause the Applicant(s) has/have defined the terms in question after Lucas made his definitions, the definitions of the Applicant(s) are the most current operable version of the definitions" (*id.* 11).[5]

We find this argument regarding the proper interpretation of the claim and prior art unpersuasive because the issue here is whether Lucas teaches "prevention of edema" as required by claim 1. Lucas expressly teaches that its compositions for "treating oedema" encompass a treatment that "prevents, ameliorates, or cures oedema, in particular pulmonary oedema" (FF 3). There is no inconsistency with Appellants' own definition. Lucas is simply explaining the terms in its patent.

There is no reasonable doubt that Lucas teaches to prevent edema. Lucas states "there is an urgent need to efficiently ***prevent*** or treat pulmonary edema" (FF 1; emphasis added). Lucas teaches that one form of treatment of edema includes preventing such edema (FF 3). Indeed, Lucas explains "the present invention aims at providing non-toxic peptides derived from TNF which can be used to ***prevent*** or treat oedema" (FF 4; emphasis added). Thus, even if we agree with Appellants that the broadest reasonable interpretation of "treating" edema need not necessarily encompass prevention, Lucas specifically teaches edema prevention (FF 1, 3, 4), satisfying the requirement of claim 1 for "prevention of edema."

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[5] We note that Appellants do not identify any specific statement in the Specification defining either the terms "treatment" or "prevention" (*see* App. Br. 11).

Appellants contend "the Current Action's characterization of TIP peptides (TIP peptides are peptides that mimic the lectin-like domain of TNF-α) in the cited documents as being inherent with respect to the method claims of the present invention is improper" (App. Br. 11). Appellants contend "that preventing the 'entry of fluid via the endothelium of the capillaries into the epithelium of the lung at the alveoli' does not 'necessarily' flow from the cited document" (*id.* 12). Appellants contend:

> This property of the TIP peptide was not used in the prior art because in the prior art the TIP peptide was never used for prevention of an edema that is not yet generated but was only used after development of edema to remove fluid after the development of the disease in an ARDS patient. Applicant(s) respectfully submit(s) that the use of TIP for the prevention of edema is not inherently a function of TIP in light of the Lucas '861 Patent

(App. Br. 13).

We find this argument unpersuasive because Lucas recognizes "there is an urgent need to prevent . . . edema" (Lucas, 1:42–43), expressly equates "treating" edema, with, among things, preventing it in the first instance (*id.* at 1:42–43, 6:7–10), and administers the exact same peptide as claim 1 to patients with the exact same disease conditions as claim 1 in overlapping dosage amounts consistent with the Specification (FF 1–8). In *Montgomery*, the drug ramipril was administered to patients in need of stroke prevention and the Court found that "efficacy is inherent in carrying out the claim steps." *In re Montgomery*, 677 F.3d 1375, 1381 (Fed. Cir. 2012). Similarly here, where Lucas teaches administration of the cyclized CGQRETPEGAEAKPWYC peptide identical to that in claim 1 to the same patient population suffering acute respiratory distress syndrome (FF 2, 4–5) in doses overlapping with those recited in claim 1 (FF 5, 7, 8) "to prevent or

treat oedema" (FF 4), we agree with the Examiner that there is a persuasive case that such peptide administration would necessarily yield the functional results recited in claim 1 of "increasing the expression of epithelial sodium channel" and "inhibiting the activation of Protein Kinase C" (*see* Ans. 14–15).

The Examiner cited evidence, Xiong[6] and Shabbir,[7] to support the inherency position (*see* Ans. 15), but we need not rely upon these references because Lucas alone reasonably shifts the burden to Appellants to demonstrate that the recited peptide, at the suggested dosages, would not necessarily result in "increasing the expression of epithelial sodium channel" and "inhibiting the activation of Protein Kinase C" because "[w]hether the rejection is based on 'inherency' under 35 U.S.C. § 102, on 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products." *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). That is, once the Examiner has provided a reasonable basis for inherency, the burden is placed on Appellants to rebut that position with evidence, not attorney argument.

At best, Appellants have recognized new properties that inherently result from administration of the cyclized CGQRETPEGAEAKPWYC

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[6] Chenling Xiong et al., *The lectin-like domain of TNF protects from listeriolysin-induced hyperpermeability in human pulmonary microvascular endothelial cells - A crucial role for protein kinase C-α inhibition*, 52 VASCULAR PHARMACOLOGY 207–13 (2010).
[7] Shabbir et al., *Mechanism of Action of Novel Lung Edema Therapeutic AP301 by Activation of the Epithelial Sodium Channel*, 84 MOLECULAR PHARMACOLOGY 899–910 (2013).

peptide to ARDS patients to "prevent . . . pulmonary edema" (FF 1), but Appellants have "done nothing more than recognize properties inherent in certain prior art . . . just like the corrosion resistance properties inherent to the prior art alloy in *Titanium Metals*." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1350–51 (Fed. Cir. 2002) (*citing Titanium Metals Corp. v. Banner*, 778 F.2d 775 (Fed. Cir. 1985). Therefore, even if Appellants have recognized something about the peptide that was not known before, the claims "do not describe a new method." *Id.* at 1352.

Appellants contend

> The method of the present invention is based on the surprising and unexpected result that TIP can be internalized, and that the internalization of TIP leads to the intracellular phosphorylation of the Myosin Light Chain in cells that have not been changed by edema, thereby preventing passage of liquid into the alveoli by increasing the expression of epithelial sodium channel and inhibiting the activation of Protein Kinase C in the endothelium of the capillaries.

(App. Br. 15).

We find this argument unpersuasive because unexpected results, a type of secondary consideration, are not an element of an anticipation analysis. *See Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) ("[S]econdary considerations are not an element of a claim of anticipation").

Conclusion of Law

A preponderance of the evidence of record support the Examiner's conclusion that Lucas teaches "prevention of edema" using the claimed peptide as required by claim 1.

SUMMARY

In summary, we affirm the rejection of claim 1 under 35 U.S.C. § 102(b) as anticipated by Lucas. Claims 6 and 13 fall with claim 1.

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