UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/756,063	01/31/2013	Jae-Il Park	STAN-679CON	7347

77974 7590 04/11/2017
Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
04/11/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JAE-IL PARK and SHEAU YU HSU[1]

Appeal 2016-003990
Application 13/756,063
Technology Center 1600

Before ERIC B. GRIMES, TIMOTHY G. MAJORS, and DAVID COTTA, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to methods of inducing labor or treating pre-eclampsia, which have been rejected as nonenabled. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm-in-part.

STATEMENT OF THE CASE

"Relaxin is a pregnancy hormone discovered in 1926." (Spec. ¶ 3.) There are seven members of the relaxin family, including "relaxin H2 (RLN2)," which signals through the receptors LGR7 and LGR8. (*Id.* ¶ 4.)

---

[1] Appellants identify the Real Party in Interest as the Board of Trustees of the Leland Stanford Junior University. (Appeal Br. 1.)

The Specification discloses "relaxin analogs . . . [that] have altered receptor specificity as compared to the reference, naturally occurring forms, e.g. wild-type human RLN2." (*Id.* ¶ 9.) The Specification states that "[t]he analogs are useful as therapeutic agents. Conditions treatable with relaxin analogs include . . . induction of labor, treatment of pre-eclampsia," etc. (*Id.* ¶ 10.) "Preeclampsia is a devastating pregnancy-associated disorder characterized by the onset of hypertension, proteinuria, and edema." (Kanasaki[2] 831.)

Claims 20 and 23–46 are on appeal. Claims 20, 25, and 36 are the independent claims and read as follows:

20. A method of inducing labor or treating pre-eclampsia, comprising administering to an individual an effective dose of a pharmaceutical formulation comprising a purified polypeptide analog of a mammalian relaxin 2 (RLN2) protein comprising an amino acid substitution to an amino acid other than the wild-type at residue 23 in the A chain, wherein the analog has increased selectivity for activation of the relaxin receptor LGR7 relative to the wild-type protein; and a pharmaceutically acceptable excipient.

25. A method of inducing labor, comprising administering to an individual an effective dose of a pharmaceutical formulation comprising a purified polypeptide analog of a mammalian relaxin 2 (RLN2) protein comprising an amino acid substitution at one or both of amino acid residues 16 and 17 to an amino acid other than the wild-type in the A chain, wherein the analog has increased activity for activation of the relaxin receptors LGR7 or LGR8 relative to the wild type protein; and a pharmaceutically acceptable excipient.

36. A method of treating preeclampsia, comprising administering to an individual an effective dose of a pharmaceutical formulation comprising a purified polypeptide analog of a mammalian relaxin 2 (RLN2) protein comprising an amino acid substitution at one or both of amino acid residues

---

[2] Kanasaki et al., *The biology of preeclampsia*, 76 Kidney Int'l 831–837 (2009). Kanasaki is one of the references cited by the Examiner.

16 and 17 to an amino acid other than the wild-type in the A chain, wherein the analog has increased activity for activation of the relaxin receptors LGR7 or LGR8 relative to the wild type protein; and a pharmaceutically acceptable excipient.

DISCUSSION

The Examiner has rejected all of the claims on appeal under 35 U.S.C. § 112, first paragraph, for lack of enablement. We will address the claims that encompass inducing labor (claims 20 and 23–35) separately from the claims limited to treating pre-eclampsia (claims 36–46).

Method of inducing labor

Claims 20 and 23–35 encompass a method of inducing labor by administering a relaxin analog. The Examiner acknowledges that the Specification states that the disclosed relaxin analogs can be used to induce labor, but notes that it does not provide any working examples that show induction of labor. (Ans. 3–4.) The Examiner finds that the "relevant literature teaches that recombinant human relaxin has no effect" in inducing labor. (*Id*. at 4.) The Examiner cites Brennand,[3] Kelly,[4] and Weiss[5] as evidence supporting this conclusion. (*Id*.)

---

[3] Brennand et al., *Recombinant human relaxin as a cervical ripening agent*, 104 British Journal of Obstetrics and Gynaecolgy 775–780 (1997).
[4] Kelly et al., *Relaxin for cervical ripening and induction of labour (Review)*, Cochrane Database Systemic Reviews 2, Article No. CD003103, pages 1–32 (2001).
[5] Weiss et al., *A Randomized, Double-Blind, Placebo-Controlled Trial of Relaxin for Cervical Ripening in Post-Delivery Date Pregnancies,* 1160 Ann. N.Y. Acad. Sci. 385–386 (2009).

We agree with the Examiner that a preponderance of the evidence of record supports a conclusion that relaxin does not induce labor, and therefore using a relaxin analog to do so would require undue experimentation. Brennand states that "porcine relaxin had some therapeutic benefit as a cervical ripening agent in women. . . . The development of recombinant human relaxin . . . has provided an agent that could have superior cervical ripening properties in women and has stimulated further research in this field." (Brennand 775, right col.)

Brennand "reports the results of the UK double-blind, three-centre study investigating the effect of recombinant human relaxin, administered as an intravaginal gel, on cervical ripening in pregnant women at term with an unfavourable cervix." (*Id.*) More specifically, Brennand's study compared a placebo to recombinant human relaxin at 1, 2, or 4 mg, administered in a gel vehicle. (*Id.* at 776, left col.)

Brennand states that

> this study has not demonstrated any cervical ripening effect of recombinant human relaxin. This may simply be due to incorrect choice of dosage. However, it seems more likely that the route of administration for this large polypeptide hormone was inappropriate. The intravenous route may be more suitable and deserves to be investigated before we can discard relaxin as a ripening agent.

(*Id.* at 779, right col.)

Weiss reports a study in which subjects received intravenously administered relaxin at a dose of 75 μg/kg/day. (Weiss 385–386, bridging paragraph.) Weiss concluded that "human relaxin infusion is safe, has positive effects on blood pressure and renal function, and does not advance cervical ripening and induce labor." (*Id.* at 386, left col.)

Kelly provides a summary of several "[c]linical trials comparing relaxin used for third trimester cervical ripening or labour induction with placebo/no treatment or other methods." (Kelly 1 (Selection criteria).) The trials studied by Kelly included Brennand. (*Id.* at 7, left cols.) Kelly found that "[c]urrently available data do not show any significant difference between relaxin and placebo for induction of labour." (*Id.* at 6, right col.) Kelly concluded that "[t]he place of relaxin, either purified porcine or recombinant human, as an induction or cervical priming agent is unclear and its use outside of clinical trials should be discouraged." (*Id.* at 6, right col.)

Thus, the three references cited by the Examiner provide experimental evidence showing that relaxin is not effective in inducing labor in pregnant women.

Appellants state that "[i]t is also known in the art that LGR7 is involved in induction of labor." (Appeal Br. 4.) In support, Appellants cite Hsu[6] and state that it was "previously made of record," although they do not indicate when. (*Id.*) The Examiner states that, "contrary to Appellant's assertion, the Hsu et al. paper has not been submitted for independent review by the Examiner." (*Id.* at 8.) Appellants did not file a Reply Brief to clarify if or when Hsu was made of record. We have therefore not considered it.

Appellants also argue that "human relaxin has currently been tested in a Phase II clinical trial for cervical ripening during the process of inducing labor, for example as described in US Clinical trials NCT00259103, sponsored by Corthera, Inc (previously submitted)." (*Id.* at 5.) Appellants

---

[6] 295 Science 671 (2002).

argue that "[o]ne of skill in the art would reasonably expect to substitute the more active or more selective polypeptides of the present invention for a known use of relaxin." (*Id.*)

The Clinical Trials reference summarizes a study in which relaxin was administered to determine its effect on "[c]ervical ripening" and "[p]rogression to active labor and delivery" i.e., induction of labor. (Clinical Trials 1, primary and secondary outcomes, respectively.) As the Examiner points out (Ans. 9), however, the reference does not report the results of the clinical trial. Rather, it merely describes the patients and procedures of the clinical trial. And, as the Examiner also points out (Ans. 9), the trial described bears a striking resemblance to the trial described by Weiss, which found that relaxin does not induce labor.

In summary, we conclude that a preponderance of the evidence of record supports the Examiner's conclusion that relaxin is not effective in inducing labor, and therefore practicing the full scope of claims 20 and 25 would require undue experimentation. We therefore affirm the rejection of claims 20 and 25 for lack of enablement.

Claims 23, 24, and 26–35 have not been argued separately and therefore fall with claims 20 and 25. 37 C.F.R. § 41.37(c)(1)(iv).

Method of treating preeclampsia

Claims 36–46 are directed to treating preeclampsia by administering a relaxin analog. The Examiner acknowledges that the Specification states that the disclosed relaxin analogs can be used to treat preeclampsia, but notes that it does not provide any working examples that show treating preeclampsia. (Ans. 3–4.) The Examiner finds that the "relevant literature

teaches that the pathophysiological mechanisms underlying the onset of pre-eclampsia are not yet fully known and defined." (*Id.* at 5.) The Examiner cites Cernaro,[7] Kanasaki,[8] and Unemori[9] as evidence supporting this conclusion. (*Id.*) In responding to Appellants' arguments, the Examiner also cites Lafayette.[10] (*Id.* at 12–13.)

Appellants argue, among other things, that

> [b]ecause reducing blood pressure in women with hypertension has been shown to prevent the progression to severe hypertension, maternal complications such as cerebrovascular hemorrhage, and heart failure, and to improve fetal maturity by prolonging pregnancy, pharmacological intervention with relaxin analogs can be used for the treatment of preeclampsia by decreasing blood pressure and vascular resistance while increasing cardiac output and placental perfusion.

---

[7] Cernaro et al., *Relaxin: New Pathophysiological Aspects and Pharmacological Perspectives for an Old Protein,* 34 Medicinal Research Reviews 77–105 (2014).
[8] Cited *supra*, footnote 2.
[9] Unemori et al., *Scientific Rationale and Design of a Phase I Safety Study of Relaxin in Women with Severe Preeclampsia*, 1160 Ann. N.Y. Acad. Sci. 381–384 (2009).
[10] Lafayette et al., *Serum relaxin levels and kidney function in late pregnancy with or without preeclampsia*, 75 Clinical Nephrology 226–232 (2011).

(Appeal Br. 6.) Appellants cite Conrad,[11] Davison,[12] Sasser,[13] and Gooi[14] as evidence supporting their position.

We agree with Appellants that a preponderance of the evidence shows that relaxin is likely to be effective in, at least, lowering blood pressure in patients suffering from preeclampsia. Several of the references state that hypertension is a symptom of preeclampsia. Kanasaki states that "[p]reeclampsia is a devastating pregnancy-associated disorder characterized by the onset of hypertension, proteinuria, and edema." (Kanasaki 831, right col.) Cernaro states that "preeclampsia [is] a pathological condition defined by the development of arterial hypertension associated with proteinuria or edema or both, due to pregnancy or to the influence of a recent pregnancy." (Cernaro 82.) Davison states that "[t]he term preeclampsia refers to the new onset of hypertension (>140/90 mmHg) and proteinuria after 20 wk of gestation in previously normotensive, nonproteinuric women." (Davison 2440, left col.)

Several of the references also state that relaxin reduces blood pressure. Weiss states that "human relaxin infusion is safe, *has positive*

---

[11] Conrad et al., *The renal circulation in normal pregnancy and preeclampsia: is there a place for relaxin?* 306 Am. J. Renal Physiol. F1121–F1135 (2014).
[12] Davison et al., *New Aspects in the Pathophysiology of Preeclampsia*, 15 J. Am. Soc. Nephrol. 2440–2448 (2004).
[13] Sasser et al., *Relaxin Ameliorates Hypertension and Increases Nitric Oxide Metabolite Excretion in Angiotensin II But Not N^{ω}-Nitro-L-Arginine Methyl Ester Hypertensive Rats*, 58 Hypertension 197–204 (2014).
[14] Gooi et al., *Enhanced Uterine Artery Stiffness in Aged Pregnant Relaxin Mutant Mice is Reversed with Exogenous Relaxin Treatment,* 89 Biology of Reproduction 1–11 (2013).

effects on blood pressure and renal function, and does not advance cervical ripening and induce labor." (Weiss 386, left col., emphasis added.) Sasser states that "the *antihypertensive* and renoprotective effects of relaxin are dependent on a functional NOS system." (Sasser 200, left col., emphasis added.) Sasser also states: "our data indicate that relaxin is a potential therapeutic agent for the treatment of hypertension." (*Id.* at 203, left col.) Cernaro states that "in the 1980s the first findings were published about relaxin's ability to induce, if administered, a decrease in blood pressure." (Cernaro 80.)

Finally, Unemori expressly suggests that relaxin should help in treating preeclampsia by lowering blood pressure. Unemori states that "[r]egardless of a potential relaxin deficiency in preeclampsia, the pharmacological effects of relaxin demonstrated in previous clinical trials and in nonclinical studies suggest that it may have a beneficial effect on blood pressure, renal function, and fetal perfusion in women with preeclampsia." (Unemori 383, bridging paragraph.)

The Examiner points to Lafayette's statement that "serum relaxin levels do 'not appear to influence BP [blood pressure], renal vascular resistance, renal blood flow, or GFR [glomerular filtration rate] in late pregnancy or in women with pre-eclampsia.'" (Ans. 12–13, quoting Lafayette 226 (abstract).) However, Lafayette is referring to endogenous levels of relaxin. It does not address the effect of administering relaxin to women with preeclampsia.

In summary, we conclude that a preponderance of the evidence does not support the Examiner's conclusion that the claimed method of treating preeclampsia would require undue experimentation.

SUMMARY

We affirm the rejection for nonenablement as applied to claims 20 and 23–35 but reverse it as applied to claims 36–46.

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-IN-PART