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.
13/312,698	12/06/2011	Robin Tuytten	LAUR005.003AUS	1590

20995 7590 02/01/2019

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER
DINES, KARLA A

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
02/01/2019	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):

jayna.cartee@knobbe.com
efiling@knobbe.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ROBIN TUYTTEN, GREGOIRE THOMAS, and PIET MOERMAN

Appeal 2017-011382
Application 13/312,698[1]
Technology Center 1600

Before ROBERT A. POLLOCK, TIMOTHY G. MAJORS, 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 test panel comprising five particular specific binding molecules conjugated to an optical detection agent, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

"Hypertensive disorders [including preeclampsia ("PE")] occurring during pregnancy represent a major cause of maternal morbidity and

---

[1] Appellants identify the real party in interest as MyCartis NV. (Appeal Br. 2.)

mortality worldwide, and are also associated with increased perinatal mortality." (Spec. 1.) "Dependable and early prediction and/or diagnosis is therefore crucial for successful treatment interventions in hypertensive disorders of pregnancy including inter alia PE." (*Id.* at 2.) "The invention relates to biomarkers and parameters useful for the diagnosis, prediction, prognosis and/or monitoring of diseases and conditions in subjects," such as PE. (*Id.* at 1.)

Claims 9, 18, 20, and 21 are on appeal. Claim 9 is representative and reads as follows:

> 9. A test panel comprising IGFALS-specific binding molecule conjugated to an optical detection agent, SPINT1-specific binding molecule conjugated to an optical detection agent, ADAM12-specific binding molecule conjugated to an optical detection agent, s-Endoglin (ENG or s-ENG) -specific binding molecule conjugated to an optical detection agent and MUC18-specific binding molecule conjugated to an optical detection agent.

(Appeal Br. 13.)

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

Claim 9 under 35 U.S.C. § 103 as unpatentable over Wewer,[2] Krizman,[3] Kim,[4] Mori,[5] López-Novoa,[6] and Liu.[7]

Claims 18, 20, and 21 under 35 U.S.C. § 103 as unpatentable over Wewer, Krizman, Kim, Mori, López-Novoa, Liu, and Rayman.[8]

Claims 9, 20, and 21 provisionally on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4, 10, 11, 14, 15, and 17–19 of copending Application No. 14/363,903.

DISCUSSION

Obviousness

The Examiner finds that Wewer teaches "an array for the determination of a protein," that "ADAM 12 is used in conjunction with biometric, serological, or clinical information to derive a risk for developing

---

[2] Wewer et al., US 2006/0134654 A1, published June 22, 2006.
[3] Krizman, US 2009/0136971 A1, published May 28, 2009.
[4] Kim et al., KR 10-2010-0088217, published Aug. 9, 2010.
[5] Mori et al., *The Cytotrophoblast Layer of Human Chorionic Villi Becomes Thinner but Maintains Its Structural Integrity During Gestation*, 76 Biology of Reproduction 164–172 (2006).
[6] José M. López-Novoa, *Soluble endoglin is an accurate predictor and a pathogenic molecule in pre-eclampsia*, 22 Nephrology Dial Transplant 712–714 (2007).
[7] Liu et al., *Pre-eclampsia is associated with the failure of melanoma cell adhesion molecule (MCAM/CD146) expression by intermediate trophoblast*, 84 Laboratory Investigation 221–228 (2004).
[8] Rayman et al., *Low selenium status is associated with the occurrence of the pregnancy disease preeclampsia in women from the United Kingdom*, 189 Am. Journal of Obstetrics and Gynecology 1343–1349 (2003).

pre[]eclampsia," and that determination of ADAM12 in a sample can be "by any detection assay known to a person of skill in the art, including immunoassays and other known arrays." (Final Action 5.) The Examiner finds that Wewer teaches that ADAM12 serum concentration was reduced in women who developed preeclampsia and is used in conjunction with biometric, serological, or clinical information to derive a risk for developing preeclampsia. (*Id.*)

The Examiner recognizes that Wewer does not teach an optical detection agent conjugated to a binding molecule for ADAM12, but notes that Krizman teaches that "protein array results are usually obtained using optical detection methods." (*Id.*) The Examiner concludes that it would have been obvious to one of ordinary skill in the art to use an optical detection agent in Wewer for the detection of ADAM12 in light of the teachings of Krizman. (*Id.* at 6.)

Regarding the inclusion of IGFALS, SPINT1, s-Endoglin, and MUC18 specific binding molecules, the Examiner finds that the prior art disclosed each as a biomarker associated with preeclampsia. (*Id.* at 5; Ans. 13.) In particular, the Examiner notes that Kim teaches IGFALS as a biomarker related to preeclampsia, Mori teaches SPINT1 as a potential specific marker for preeclampsia; López-Novoa teaches s-Endoglin as a promising marker to presage preeclampsia, and Liu teaches MUC18 has a different pattern of expression in normal pregnancy and in preeclampsia where it is reduced in placentas as compared to those placentas not complicated by preeclampsia. (Final Action at 5–6.) The Examiner concludes that it would have been obvious to combine these biomarkers for use in a panel of biomarkers to "attain[] better predictability" (Ans. 13),

"because Wewer et al. teach the use of a biomarker in conjunction with other biometric, serological, or clinical information to derive a risk for developing preeclampsia," and "in the interest of operational efficiency, saving time and resources by testing more than one biomarker at a time" (Final Action 6).

We agree with the Examiner's factual findings and conclusion that it would have been obvious to combine into a single array the biomarkers IGFALS, SPINT1, ADAM12, ENG/s-ENG and MUC18 taught by the prior art, and to have conjugated each to an optical detection agent.

Appellants admit that "the biomarkers IGF ALS, SPINT1, ADAM12, ENG/s-ENG and MUC18 were taught in the prior art" but contend that "not all of them were presented as solutions with respect to predicting preeclampsia" and thus "the art does not teach 'predictable solutions' as asserted by the Examiner." (Appeal Br. 7; *see also* Appeal Br. 8–9 ("the references do not teach that these markers can predictably be used to predict preeclampsia, either separately or together.").) Appellants note that Wewer teaches that "ADAM12 serum levels are reduced in the first semester of Down's syndrome and trisomy 18 pregnancies, as well as in pregnancies that later developed preeclampsia ([0032]) . . . [and its] overexpression correlates to cancer formation." (*Id.* at 8) (emphasis omitted.) Thus, Appellants assert that Wewer teaches that changes in serum levels of ADAM12 "may be useful for screening pathologies in pregnant and non-pregnant individuals ([0005])." (*Id.*) (emphasis omitted.)

Further, Appellants note that while Mori indicates that it would be of interest to use SPINT1 for preeclampsia, "there is no teaching that SPINT1 presence or level is actually correlated to preeclampsia." (*Id.*) And, Appellants argue that the remaining references only note "some association

with the described marker and preeclampsia is disclosed," but do not indicate that preeclampsia can be predicted using the marker. (*Id.*)

We do not find Appellants' arguments persuasive because, as the Examiner explained, the claims are directed to a test panel and not a method for its use. (Ans. 13.) Thus, the Examiner need not establish the combination of biomarkers would, when tested for, predict preeclampsia. Appellants do not contest that the 5 biomarkers were known in the art to be related to preeclampsia.[9] Nor do Appellants contest the Examiner's assertion (Ans. 16) that it is customary practice in assessing medical conditions to combine multiple biomarkers and test for their presence. We conclude in light of the foregoing, that the Examiner has established a reason to combine the biomarkers into a single test panel, even if they were not yet established individually to be predictive of preeclampsia. That is, a reason to combine the biomarkers would be to study their relationship together as predictors for preeclampsia, or to use them in diagnosing preeclampsia with

---

[9] In their Reply Brief, Appellants contest the Examiner's assertion in the Examiner's Answer that Appellants admitted the five biomarkers recited in claim 9 were known in the art to be related to preeclampsia. (Reply Br. 1.) Appellants quote the paragraph the Examiner relied on, which is as follows:

> *The Appellant nevertheless submits that, although the biomarkers IGF ALS, SPINT1, ADAM12, ENG/s-ENG and MUC18 were taught in the prior art, not all of them were presented as solutions with respect to predicting preeclampsia. That is, the art does not teach "predictable solutions" as asserted by the Examiner.*

(*Id.*, quoting Appeal Br. 7.) Appellants explain further: "the markers were known, but it was not known that these markers could be used to *predict preeclampsia*." (*Id.* at 2 (emphasis added).) We find Appellants' statements in the Appeal Brief and the Reply Brief to mean that the markers were not known to "predict preeclampsia," not that they were not known to be related to preeclampsia.

better predictability by assessing them in combination. And as the Examiner explained, operational efficiency of testing more than one biomarker at a time would have provided a reason to use them together rather than separately. The Examiner's reasoning applies even though ADAM12 is associated with other indications in addition to preeclampsia (Appeal Br. 8). That is because, in combination with other markers associated with preeclampsia, the presence of ADAM12 would be helpful in confirming preeclampsia.

Appellants argue that "simply combining molecules that are specifically binding to known biomarkers will not necessarily provide a tool enabling optimal accuracy in the detection of disease." (Appeal Br. 11.) This argument is not persuasive as the claims do not require optimal accuracy in detecting preeclampsia. Moreover, "just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes." *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012). Thus, whether combining these markers would result in an optimal combination is not dispositive of the obviousness question. The Examiner has provided a prima facie case of obviousness presenting an objective reason why one of ordinary skill in the art would have combined these markers in a single test panel.

Appellants further argue that accuracy of the combination of markers in combination with blood pressure measurement was unexpected (1) with respect to the prediction of preeclampsia as shown in the tables in the Specification and (2) that the Declaration of Grégoire Thomas submitted April 8, 2015 demonstrates "that the combination of markers as claimed is unexpectedly better than the use of just two markers (blood pressure and

IGFALS)." (Appeal Br. 9–10.) We note that in both sets of arguments the alleged unexpectedly better result is arrived at when the markers are measured in combination with blood pressure, which is not a recitation of the claim. Moreover, the unexpected results is in the prediction of preterm preeclampsia, also not a recitation of the claim. Thus, the arguments of unexpected results are not persuasive as the showing is not commensurate in scope with the claims. *In re Lindner*, 457 F.2d 506, 508 (CCPA 1972)("It is well established that the objective evidence of nonobviousness must be commensurate in scope with the claims."

For the reasons discussed, Appellants do not persuade us that the Examiner erred in maintaining the obviousness rejection of claim 9.

Claims 18, 20, and 21 have not been argued separately. (*See* Appeal Br. 11–12 ("Appellant[s] respectfully submit[] that the dependent claims incorporate by reference all the limitations of the claim to which they refer and include their own patentable features, and are therefore in condition for allowance.") Separately arguing a claim requires "more substantive arguments in an appeal brief than a mere recitation of the claim elements and a naked assertion that the corresponding elements were not found in the prior art." *In re Lovin*, 652 F.3d 1349, 1357 (Fed. Cir. 2011). Claims 18, 20, and 21 fall with claim 9. 37 C.F.R. § 41.37(c)(1)(iv).

Obviousness-Type Double Patenting

Appellants do not contest the provisional obviousness-type double patenting rejection. (Appeal Br. 12.) Therefore, we summarily affirm that rejection.

SUMMARY

We affirm the rejection of claim 9 under 35 U.S.C. § 103 as unpatentable over Wewer, Krizman, Kim, Mori, López-Novoa, and Liu.

We affirm the rejection of claims 18, 20, and 21 under 35 U.S.C. § 103 as unpatentable over Wewer, Krizman, Kim, Mori, López-Novoa, Liu, and Rayman.

We affirm the provisional rejection of claims 9, 20, and 21 on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4, 10, 11, 14, 15, and 17–19 of copending Application No. 14/363,903.

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