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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ARSENI MARKOV, NADJA BOGDANOVA, and VOLKER GERKE[1]

Appeal 2018-000182
Application 13/819,291
Technology Center 1600

Before RICHARD M. LEBOVITZ, ULRIKE W. JENKS, and TAWEN CHANG, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method for diagnosing or detecting a predisposition to recurrent pregnancy loss (RPL), preeclampsia (PE), and/or fetal growth restriction (FGR), which have been rejected as directed to patent-ineligible subject matter and as non-enabled. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] Appellants identify the Real Party in Interest as Universitaetsklinikum Muenster. (Appeal Br. 4.)

STATEMENT OF THE CASE

The Specification states that Annexin A5 is known as a placental anticoagulant protein, and that "[l]owered annexin A5 expression on placental trophoblast villi has been . . . confirmed in patients with preeclampsia." (Spec. 1:31–34.) The Specification also states that a sequence variation (the M2 haplotype) in the ANXA5 gene promoter reduces the activity of the promoter and represents a risk factor for recurrent pregnancy loss, pregnancy-related hypertensive disorders risk, and early fetal loss events. (*Id.* at 1:34–2:2, 2:5–8.) The Specification further states that, in comparison to controls, expression of ANXA5 mRNA in placentas was decreased in M2 haplotype carriers and in women with obstetric complications such as preeclampsia and fetal growth restriction. (*Id.* at 2:2–5.) According to the Specification,

> The present invention relates to a method for diagnosing or detecting a predisposition of a female subject to recurrent pregnancy loss (RPL), preeclampsia (PE) and/or fetal growth restriction (FGR), comprising examining the human annexin A5 (ANXA5) promoter in a sample obtained from the intended biological father or the biological father and to detect nucleotide exchanges therein, wherein the presence of [certain] nucleotide exchanges . . . indicates a predisposition of said female subject to recurrent pregnancy loss (RPL), preeclampsia (PE) and/or fetal growth restriction (FGR).

(Spec. 1:13–19.)

Claims 1–5, 7, 17–22, and 24–29 are on appeal. Claim 1 is illustrative and reproduced below:

> 1. A method for diagnosing or detecting a predisposition of a human female subject to recurrent pregnancy loss (RPL), preeclampsia (PE) and/or fetal growth restriction (FGR), comprising:

(a) obtaining a sample from a (intended) biological father, a chorion biopsy, an amniocentesis sample obtained from a human female subject, or a single cell sample obtained before or during the morula stadium of an *in vitro* fertilized embryo prior to its implantation into a human female subject;
(b) processing the sample to provide a nucleic acid comprising a human annexin A5 (ANXA5) promoter sequence from the sample;
(c) preparing a composition comprising (i) the nucleic acid comprising the human annexin A5 (ANXA5) promoter sequence and (ii) a nucleic acid that hybridizes to at least a portion of (i)
(d) detecting nucleotide exchanges (1)-(4):

(1) G to A at a position which corresponds to nucleotide 186 of SEQ ID No.2,
(2) A to C at a position which corresponds to nucleotide 203 of SEQ ID No. 2,
(3) T to C at a position which corresponds to nucleotide 229 of SEQ ID No. 2, and
(4) G to A at a position which corresponds to nucleotide 276 of SEQ ID No. 2;

using the composition of step (a); and
(e) diagnosing or detecting the predisposition of the human female subject to RPL, PE and/or FGR if the nucleotide exchanges defined in (d) are detected in the composition.

(Appeal Br. 20 (Claims App.).)

The Examiner rejects claims 1–5, 7, 17–22, and 24–29 under 35 U.S.C. § 101 as directed to patent-ineligible subject matter. (Ans. 2.)

The Examiner rejects claims 1–5, 7, 17–22, and 24–29 under 35 U.S.C. § 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as lacking in enablement commensurate with the scope of the claims. (Ans. 8–9.)

The Examiner rejects claims 1–5, 7, 17–22, and 24–29 under nonstatutory obviousness-type double patenting as being unpatentable over claims 1–17 of U.S. Patent No. 8,119,341. (Ans. 14.)

I.

Issue

The Examiner rejected claims 1–5, 7, 17–22, and 24–29 as being directed to an abstract idea, a law of nature and a natural phenomenon. (Ans. 4.) In particular, the Examiner finds that "claim 1 is directed to 'a method for diagnosing or detecting a predisposition of a female subject to RPL, PE or FGR by examining the ANXA5 promoter for [the M2 haplotype] in a subject to diagnose or detect RPL, PE or FGR,'" and "[a] correlation that preexists in the human body is an unpatentable phenomenon." (*Id.*) The Examiner also finds that the steps in the claims relating to detecting nucleotide exchanges and diagnosing a subject's predisposition to RPL, PE and/or FGR are directed to an abstract mental process. (*Id.* at 4–5.) The Examiner finds that claims do not provide a method that is significantly more than a statement of a law of nature because they neither apply the natural law using any particular machine nor contain any specific limitation "other than what is well-understood, routine and conventional in the field." (*Id.* at 5.)

Appellants contend that "[t]he steps of obtaining, processing, preparing, and detecting [in claim 1] cannot be construed to be 'abstract mental processes.'" (Appeal Br. 14.) Appellants contend that the claims meet the machine or transformation test. (*Id.*) Appellants contend that, even if the claims are directed to a patent-ineligible concept, "the additional elements when viewed in combination amount to *significantly more* than any

asserted exception by meaningfully limiting such judicial exception." (*Id.*) Appellants contend that the claims "[do] not 'preempt' the entire field within the context of diagnosing or detecting a predisposition of a human female subject to RPL, PE, and/or FGR." (*Id.*)

The issue with respect to this rejection is whether a preponderance of the evidence of record supports the Examiner's conclusion that claims 1–5, 7, 17–22, and 24–29 are directed towards judicial exceptions to statutory subject matter, without significantly more.

Analysis

Unless otherwise noted, we adopt the Examiner's findings of fact and reasoning regarding the Examiner's rejection of claims 1–5, 7, 17–22, and 24–29 under 35 U.S.C. § 101 (Final Act. 4–13; Ans. 2–8, 15–22) and agree that the claims are unpatentable as being directed to a judicial exception without significantly more. Only those arguments timely made by Appellants in the Appeal Brief (no Reply Brief was submitted) have been considered; arguments not so presented in the Brief are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived."). We highlight the following points for emphasis.

We analyze this case under the framework set forth by the Supreme Court in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012), and applied by our reviewing court in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015). As the *Ariosa* court explained:

> In *Mayo* . . . , the Supreme Court set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts. First, we determine whether the claims at issue are directed to a patent-ineligible concept. . . . If the answer is yes, then we next consider the elements of each claim both individually and "as an ordered combination" to determine whether additional elements "transform the nature of the claim" into a patent-eligible application. . . . The Supreme Court has described the second step of this analysis as a search for an "inventive concept"—i.e., an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."

Id. at 1375.

We begin with the first step of the *Mayo* test, namely whether a claim is "directed to" a patent-ineligible concept. On January 7, 2019, the Director of the USPTO issued the "2019 Revised Patent Subject Matter Eligibility Guidance" ("Revised Guidance"), which provides further details regarding how the Patent Office analyzes patent-eligibility questions under 35 U.S.C. § 101. 84 Fed. Reg. 50–57 (Jan. 7, 2019). Under the Revised Guidance, the first step of the *Mayo* test (i.e., Step 2A of the Revised Guidance) is "a two-pronged inquiry." *Id.* at 54. In prong one, we evaluate whether the claim recites a judicial exception, such as laws of nature, natural phenomena, or abstract ideas. *Id.* If the claim recites a judicial exception, the claim is further analyzed under prong two, which requires "evaluat[ion of] whether the claim recites additional elements that integrate the exception into a practical application of that exception." *Id.* The Revised Guidance explains that, "[i]f the recited exception is integrated into a practical application of

the exception, then the claim is eligible at Prong Two of . . . Step 2A [of the Revised Guidance]." *Id.*

With respect to the first prong of Step 2A of the Revised Guidance, we agree with the Examiner that claim 1 recites a patent-ineligible law of nature, specifically, the relationship between the presence of certain nucleotide exchanges and a predisposition to RPL, PE and/or FGR as specifically recited in step (e) of the claim. (Ans. 4.) In *Mayo*, for instance, the Supreme Court found that a claim was directed to a natural law, where the claim required administering a drug and determining the levels of a metabolite following administration, where the level of metabolite was indicative of a need to increase or decrease the dosage of the drug. *See Mayo Collaborative Services v. Prometheus Labs., Inc.*, 566 U.S. 66, 74 (2012). Here, similarly, claim 1 recites "diagnosing or detecting the predisposition of the human female subject to RPL, PE and/or FGR if the nucleotide exchanges defined in [step] (d) are detected."

Appellants contend that "[t]he steps of obtaining, processing, preparing, and detecting [in claim 1] cannot be construed to be 'abstract mental processes'" and that "[t]o assert the claim broadly encompasses mental activities and therefore is directed to an abstract idea ignores the material features of a 'sample,' 'a nucleic acid,' a 'composition' according to the claims." (Appeal Br. 14.)

We are not persuaded. The Examiner did not reject claim 1 on the ground that *all* of the claimed steps are "abstract mental processes." Rather, the Examiner found the claim to be patent-ineligible because it is directed to a law of nature and natural phenomenon, namely "[a]n association between SNPs in ANXA5 and RPL, PE and/or FGR," while steps (d) and (e), relating

to detecting certain nucleotide exchanges and diagnosing predisposition to RPL, PE and/or FGR, are also abstract mental processes. (Ans. 4–5.) Appellants have not disputed, much less persuasively rebutted, the Examiner's conclusion that the claim recites a law of nature and natural phenomenon.[2]

With respect to the second prong of Step 2A of the Revised Guidance, we find that claim 1 does not recite "additional elements that integrate the exception into a practical application of that exception." 84 Fed. Reg. at 54. Unlike the claims in *Vanda Pharmaceuticals*, and like the claims in *Mayo*, claim 1 is not directed to a method of treating disease but to a diagnostic method based on a natural relationship between the presence of certain nucleotide exchanges in the ANXA5 promoter sequence and a predisposition to RPL, PE and/or FGR. *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1134–1135 (Fed. Cir. 2018).

Appellants contend that claim 1 meets the machine or transformation test because not all of the steps of claim 1 can be construed as abstract

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[2] The Examiner does conclude that the steps of "detecting nucleotide exchanges (1)–(4)" and "diagnosing or detecting the predisposition of the human female subject to RPL, PE and/or FGR" are abstract mental processes and state that, "[a]s the claims broadly encompass mental activities they are considered to be directed to an abstract idea." (Ans. 4–5, 15–16.) Although we agree that mental processes are not patent-eligible, *Mayo*, 566 U.S. at 71, we disagree with and do not adopt the Examiner's statements to the extent they imply that a claim is patent-ineligible so long as it includes any patent-ineligible concept. *See, e.g., Diamond v. Diehr*, 450 U.S. 175, 192 (1981) (holding that a claim containing a mathematical formula is nevertheless patent-eligible when the claim, "considered as a whole, is performing a function which the patent laws were designed to protect").

mental processes and because the claim recites tangible materials such as a sample, a nucleic acid, and a composition. (Appeal Br. 14.)

We are not persuaded. Under the machine-or-transformation test, a process may be patent-eligible under § 101 if "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." *In re Bilski*, 545 F.3d 943, 954 (Fed. Cir. 2008). Our reviewing court has further explained that "a machine is a concrete thing, consisting of parts, or of certain devices and combination of devices," and that "[t]his includes every mechanical device or combination of mechanical powers and devices to perform some function and produce a certain effect or result." *In re Ferguson*, 558, F.3d 1359, 1364 (Fed. Cir. 2009) (internal quotation marks and citations omitted).

Here, as the Examiner points out, Appellants have not pointed to any concrete parts, devices, or combination of devices required by claim 1. (Ans. 21.) For instance, claim 1 does not recite any particular machine to be used to obtain a sample, to process the sample to provide a nucleic acid comprising a human ANXA5 promoter sequence, to prepare a composition comprising said nucleic acid and a hybridizing nucleic acid, to detect recited nucleotide exchanges, or to diagnose or detect a subject's predisposition to RPL, PE and/or FGR. Similarly, Appellants have failed to identify how any article is transformed into "a different state or thing" in its process.

Moreover, even if claim 1 involved the use of a particular machine or the transformation of an article, the Federal Circuit has explained that "the use of a specific machine or transformation of an article must impose meaningful limits on the claim's scope to impart patent-eligibility," and "the involvement of the machine or transformation in the claimed process must

not be insignificant extra-solution activity." *In re Bilski*, 545 F.3d at 961–962. Likewise, the Supreme Court has clarified that, even though "the 'machine-or-transformation' test is an '*important and useful clue*' to patentability," the test does not "trump[] the 'law of nature' exclusion." *Mayo*, 566 U.S. at 1303. Thus, for the reason discussed below, claim 1 would not be patent eligible even if Appellants can identify some involvement of a machine or some transformation in the claimed process.

Having determined that claim 1 is directed to a patent-ineligible law of nature, we next consider whether claim 1 recites "an element or combination of elements that is 'sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.'" *Ariosa*, 788 F.3d at 1375 (citation omitted). We agree with the Examiner that it does not. (Ans. 5–6.) The Examiner finds, and Appellants have not persuasively disputed, that "[t]he claims . . . do not add a specific limitation other than what is well-understood, routine and conventional in the field." (*Id.* at 5.) For instance, as the Examiner points out, the Specification explicitly teaches that "means and methods to determine and/or to detect . . . risk haplotype[M2] are well-known." (*Id.* at 5–6 (internal quotation marks omitted); Spec. 5:27–28.) Likewise, as the Examiner also points out, each of the manipulative steps in claim 1 are disclosed in the prior art. (*Id.* at 6.) Bogdanova,[3] for instance, teaches extracting genomic DNA from peripheral blood lymphocytes (i.e., obtaining sample and processing sample to provide nucleic acid); amplifying genomic

[3] Nadia Bogdanova et al., *A Common Haplotype of the Annexin A5 (ANXA5) Gene Promoter Is Associated With Recurrent Pregnancy Loss*, 16 HUMAN MOLECULAR GENETICS 573 (2007).

DNA of interest using PCR (i.e., preparing composition comprising ANXA5 promoter sequence and hybridizing nucleic acid); and sequencing the amplicons (i.e., detecting nucleotide exchanges). (Bogdanova 577, left column.) Chinni[4] likewise teaches processing samples to extract DNA, amplifying genomic DNA of interest using PCR, and sequencing the amplified DNA fragments. (Chinni 940, right column.) Accordingly, we find that instant claim 1 is analogous to the claim found unpatentable in *Mayo*.

Appellants contend that, even if claim 1 is directed to a patent-ineligible concept, "the selection of a sample from a particular sample group according to the claim, the use of a particular nucleic acid comprising a human annexin A5 (ANXA5) promoter sequence from the sample, the preparation of a hybridization composition . . . , and the detection of the nucleotide substitution from the composition, adds significantly more when viewed in combination as opposed to those features viewed in isolation." (Appeal Br. 14)

We are not persuaded. Considering the steps of claim 1 together as an ordered combination "adds nothing to the laws of nature that is not already present when the steps are considered separately." *Mayo*, 566 U.S. at 79. Similar to the situation in *Mayo*, anyone who wants to make use of the claimed law of nature – in this case the correlation between (1) the recited nucleotide exchanges in paternal DNA, chorion material, and embryonic DNA and (2) predisposition of the mother to RPL, PE, and FGR – must

[4] Elena Chinni et al., *Annexin V Expression in Human Placenta is Influenced by the Carriership of the Common Haplotype M2*, 91 FERTILITY AND STERILITY 940 (2009).

perform the claimed steps of obtaining a sample from the (intended) father or the embryo and detecting the existence of the nucleotide exchanges. *See id.* Thus, as in *Mayo*, the combination in claim 1 "amounts to nothing significantly more than an instruction to doctors to apply the applicable laws when treating their patients." *Id.*

Appellants contend that Bogdanova and Chinni do not support the Examiner's finding that the claims do not add a specific limitation to the law of nature other than what is well-understood, routine and conventional in the field. (Appeal Br. 17.) In particular, Appellants contend that Bogdanova and Chinni do not teach "genotyping of *non-maternal samples*" for purposes of "diagnosing or detecting the RPL, PE or FGR-risk of a woman according to Appellant[s'] claim 1." (*Id.*)

We are not persuaded. Appellants essentially argue that prior art does not disclose that predisposition of a woman to RPL, PE or FGR during pregnancy may be determined by the presence of certain nucleotide exchanges in the DNA of the father of the child. The correlation between certain nucleotide exchanges in paternal DNA and predisposition of the child's mother to PRL, PE or FGR, however, is a law of nature, and cannot impart patentability to the claims even if it was previously unknown. As the Supreme Court explained in the context of mathematical algorithms,

> [t]he process itself, not merely the mathematical algorithm, must be new and useful. Indeed, the novelty of the mathematical algorithm is not a determining factor at all. Whether the algorithm was in fact known or unknown at the time of the claimed invention, as one of the "basic tools of scientific and technological work," it is treated as though it were a familiar part of the prior art.

Parker v. Flook, 437 U.S. 584, 591–592 (1978).

Finally, Appellants contend that claim 1 "does not 'preempt' the entire field within the context of diagnosing or detecting a predisposition of a human female subject to RPL, PE, and/or FGR," because "other options are available for determining the nucleotide exchange (1)-(4)." (Appeal Br. 14–15.)

We are not persuaded. "While preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility." *Ariosa*, 788 F.3d at 1379. In *Ariosa*, for instance, our reviewing court held various dependent claims to be invalid as directed to patent-ineligible subject matter, even though these claims are limited to specific techniques of amplifying and detecting nucleic acid. *See id.* at 1374, 1378 (finding invalid dependent claims requiring amplification of nucleic acid by polymerase chain reaction or detection of nucleic acid via a sequence specific probe because they are "focused on the use of the natural phenomenon in combination with well-understood, routine, and conventional activity").

Accordingly, we affirm the Examiner's rejection of claim 1. With respect to independent claim 28 and dependent claims 2–5, 7, 17–21, and 24–27, other than relying on arguments made with respect to claim 1, Appellants only recite the different or additional claim limitations and then allege with little explanation that the claim thus amounts to "significantly more" than the patent ineligible concept and/or does not "'preempt' the entire field within the context of diagnosing or detecting a disposition of a human female subject to RPL, PE, and/or FGR." (Appeal Br. 15–17.) These conclusory argument do not suffice to constitute separate argument of the claims. *Cf. In re Lovin*, 652 F.3d 1349, 1357 (Fed. Cir. 2011) ("[T]he

Board [has] reasonably interpreted Rule 41.37 to require 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."). Accordingly, claims 2–5, 7, 17–21, and 24–28 fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv). Likewise, Appellants did not separately address claims 22 and 29. They also fall with claim 1. *Id.*

II.

Issue

The Examiner rejects claims 1–5, 7, 17–22, and 24–29 as lacking in enablement commensurate with the scope of the claims. The Examiner finds that the Specification, "while being enabling for methods of detecting the M2 haplotype in maternal and paternal samples, does not reasonably [enable] a method of diagnosing or detecting a predisposition of a female subject to RPL, PE, or FGR by examining the M2 haplotype." (Ans. 8–9.)

Appellants contend that "data of the application demonstrate the relationship between M2 haplotype in non-maternal samples and FGR/RPL." (Appeal Br. 18.) Appellants further contend that, "even if only very few samples would have been analyzed in the present application, the data in . . . post-published documents clearly underline the correlation between M2 haplotype in non-maternal samples and RPL, PE and FGR as disclosed in the application." (*Id.*)

The issue with respect to this rejection is whether a preponderance of the evidence of record supports the Examiner's conclusion that the claims are invalid for failing to comply with the enablement requirement.

Analysis

On balance, we find Appellants to have the better argument. The Examiner does not dispute that the Specification is enabling with respect to detection of the M2 haplotype in maternal and paternal samples and asserts only that it does not enable a skilled artisan to diagnose or detect a predisposition to RPL, PE, or FGR based on the presence of the M2 haplotype. (Ans. 8–9.) Thus, the Examiner's rejection appears to be based on the conclusion that the Specification does not enable a skilled artisan to use the invention as claimed.

The initial burden of presenting a prima facie case of unpatentability on any ground rests on the Examiner. *See In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

We find that the PTO has not met this initial burden. The Specification explicitly states that "the risk haplotype M2 . . . is predictive for recurrent pregnancy loss (RPL), preeclampsia (PE) and/or fetal growth restriction (FGR) in a female subject" and further states that the genetic material that may be tested to determine such predisposition may be from the biological father of the embryo, or the embryo itself, as well as from the biological mother. (Spec. 4:30–5:4.)

The Examiner asserts that the invention is in an unpredictable art and, citing Hirschhorn,[5] Ioannidis,[6] and Meyer,[7] asserts that the prior art teaches that "genetic variations and associations are often irreproducible" and that "presence of [single nucleotide polymorphisms (SNPs)] in the same gene

[5] Joel N. Hirschhorn et al., *A Comprehensive Review of Genetic Association Studies*, 4 GENETICS IN MEDICINE 45 (2002).
[6] John P.A. Ioannidis et al., Letter, *Replication Validity of Genetic Association Studies*, 29 NATURE GENETICS 306 (2001).
[7] Meyer et al., US 2003/0092019 A1, published May 15, 2003.

does not indicate that each of the [SNPs] is associated with the same diseases." (Ans. 9–11.) However, Hirschhorn, Ioannidis, and Meyer do not relate specifically to the correlation between genetic variation in ANXA5 and PE, RPL, and FGR. Thus, we are not convinced that a skilled artisan would reasonably doubt the correlation asserted in the Specification based on these references.

With respect to ANXA5 specifically, the Examiner cites Ota[8] in asserting that the M2 haplotype cannot be predictably used to diagnose pre-eclampsia. (Ans. 11.) The Examiner asserts that the p-value disclosed in Ota (0.056) for the association of placental M2 haplotype (A–C–C–A) with preeclampsia shows that "no statistical association at 95% confidence is found." (*Id.*) The Examiner also points to Ota's teaching that M2 haplotype in maternal blood samples, as opposed to placental samples, was not significantly correlated with preeclampsia. (*Id.*) The Examiner asserts that it is unpredictable whether paternal and amniocentesis samples would be similar to placental samples or maternal blood samples. (*Id.*) The Examiner further asserts that Ota is silent with respect to any correlation between the M2 haplotype and RPL and FGR. (*Id.*)

We are not persuaded. While Ota does teach a *P*-value of 0.056 for the association of M2 haplotype with pre-eclampsia, Ota also teaches that

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[8] S. Ota et al., *Contribution of Fetal ANXA5 Gene Promoter Polymorphisms to the Onset of Pre-eclampsia*, 34 PLACENTA 1202 (2013). We note that Ota was accepted for publication in September 2013 and thus is published after the effective filing date of the instant application. We need not decide whether the Examiner's reliance on Ota to show non-enablement is proper, however, both because Appellants did not raise this argument, and because, as discussed below, we find that Ota does not support the Examiner's non-enablement argument.

"[t]he M2 haplotype was . . . significantly frequent in placentas from pre-eclamptic patients relative to the controls (25.5% versus 10%, $P = 0.044$)." (Ota Abstract, Tables 2 & 3.) Ota further concludes that, "[a]lthough preliminary, these results suggest that hypomorphic M2 alleles in the . . . placental ANXA5 promoter, whether transmitted maternally or paternally, might be an essential determinant of an increased risk of pre-eclampsia via local thrombophilia at the feto-maternal interface." (*Id.*) Given Ota's own interpretation of its results, we are not convinced that a skilled artisan would, based on Ota, reasonably doubt the correlation between at least the placental M2 haplotype and predisposition to pre-eclampsia.

The Examiner also appears to assert in the alternative that, even if Ota supports the existence of a correlation between placental M2 haplotype and predisposition of the biological mother to pre-eclampsia, the claims encompass using any sample from "a (intended) biological father, a chorion biopsy, [or] an amniocentesis sample," and Ota shows that M2 haplotype in some samples – e.g., the maternal blood sample – does not correlate with a predisposition to preeclampsia. (Ans. 11.) Thus, the Examiner appears to conclude, the Specification does not enable the full scope of the claim. (*Id.*)

While we acknowledge the Examiner's line of reasoning, we are not persuaded. As an initial matter, we note that Ota concluded that the lack of statistical association with the maternal allele in its results is likely due to the small number of samples. (Ota 1208, right column.) Moreover, in discussing the results of its study Ota concludes not only that "the placental . . . genotype is associated with pre-eclampsia" but also suggests that "paternal genomic variants could well contribute to this disorder since the fetal and placental genomes are 50% maternal and 50% paternally derived

and . . . the paternal genome is more important in the development of the placenta." (*Id.*) Ota further cites to a report that "a paternal M2 haplotype confers an equal risk of recurrent pregnancy loss as maternal M2," without casting doubt on the report. (*Id.*) Given Ota's own conclusions, we agree with Appellants that Ota would not have led a skilled artisan to reasonably doubt the claimed correlation between (1) the presence of M2 haplotype in paternal and fetal (chorion biopsy and amniocentesis) samples and (2) a predisposition to certain obstetric complications such as pre-eclampsia.

We are also not persuaded by Examiner's assertions that Ota at most relates to a correlation between the M2 haplotype and preeclampsia and that this correlation cannot be extrapolated to RPL and FGR. Ans. 11. Even if Ota is silent as to a correlation between the M2 haplotype and FGR and/or RPL, it does not suffice to show that the claims are not enabled because silence in Ota would not lead a skilled artisan to "reasonably doubt" the correlations asserted in the Specification. Furthermore, while Ota does not specifically investigate the correlation between the M2 haplotype and FGR and/or RPL, it states that "[c]onsiderable data have recently been accumulated concerning the association of ANXA5 promoter polymorphisms with various obstetric complications such as recurrent pregnancy loss, preeclampsia and pregnancy-related thrombophilic disorder." (Ota 1208, left column.) Likewise, Ota teaches that "reduced placental ANXA5 levels have also been reported at the mRNA level in fetal growth restriction." (*Id.*)

The Examiner asserts that the data cited in the Specification is insufficient to show the claimed correlation between the M2 haplotype and predisposition to RPL, PE, and FGR and asserts that "[t]he guidance

provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instruction to make and use the claimed invention." (Ans. 11–12.) The Examiner finds that a "significant inventive effort" would be required to practice the invention, without any guarantee that the invention in fact works as claimed (i.e., that a correlation in fact exists between the M2 haplotype and a predisposition to PE, RPL, and FGR). (*Id.* at 12.)

We are not persuaded. "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." *In re Armbruster*, 512 F.2d 676, 678 (CCPA 1975). Instead, as discussed above, "it is incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971).

Finally, although the Examiner acknowledges that Rogenhofer,[9] Tuttelmann,[10] Demetriou,[11] and Hock[12] "appear to support . . . association of

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[9] Nina Rogenhofer et al., *Paternal and Maternal Carriage of the Annexin A5 M2 Haplotype are Equal Risk Factors for Recurrent Pregnancy Loss: A Pilot Study*, 98 FERTILITY AND STERILITY 383 (2012).
[10] Frank Tuttelmann et al., *Further Insights into the Role of the Annexin A5 M2 Haplotype as Recurrent Pregnancy Loss Factor, Assessing Timing of Miscarriage and Partner Risk*, 100 FERTILITY AND STERILITY 1321 (2013).
[11] Charalambos Demetriou et al., *Investigation of the Annexin A5 M2 Haplotype in 500 White European Couples Who Have Experienced Recurrent Spontaneous Abortion*, 31 REPRODUCTIVE BIOMEDICINE ONLINE 681 (2015).
[12] Tang Thean Hock, *M2/ANXA5 Haplotype as a Predisposition Factor in Malay Women and Couples Experiencing Recurrent Spontaneous Abortion: A Pilot Study*, 30 REPRODUCTIVE BIOMEDICINE ONLINE 434 (2015).

the paternal M2 allele and RPL," the Examiner asserts that they "fail to establish the enablement of the invention at the time the invention was made" because they were published after the filing date of the application. (Ans. 24.) The Examiner also asserts that these publications are directed only to association of paternal M2 allele and RPL and do not provide any support for [preeclampsia] (PE) or fetal growth restriction (FGR). (*Id.*) The Examiner asserts that, indeed, one or more of the cited references suggest that "[a]bsent [further] experimentation, it is unpredictable the M2 haplotype is associated with . . . pregnancy pathologies" other than RPL. (*Id.* at 24–25.)

We are not persuaded. As an initial matter, the Examiner has not established a prima facie case of non-enablement because the Examiner has not provided persuasive evidence showing that a skilled artisan would reasonably doubt the asserted utility of the claims – i.e., using the presence of the M2 haplotype in paternal or fetal genotype to diagnose a predisposition of the biological mother to PE, RPL, and FGR. Thus, Appellants need not provide rebuttal evidence.

Moreover, while post-filing declaration may not be used to "render an insufficient disclosure enabling," such declaration may be used to show the accuracy of a statement in the Specification. *In re Brana*, 51 F.3d 1560, 1567 n. 19 (Fed. Cir. 1995). In this case, the post-filing references cited by Appellants perform the same function as the declaration in *In re Brana*, namely to show the accuracy of the assertion in the Specification that the M2 haplotype in paternal or fetal genotype is useful in diagnosing predisposition to PE, RPL, and FGR.

Finally, we are not persuaded by the Examiner's apparent argument that the full scope of the claims are not enabled because the post-filing references relate only to RPL. The Examiner asserts that "[t]hese three fetal prenatal conditions [(i.e., PE, RPL, and FGR)] are not related and would not be expected to be similarly associated with the M2 haplotype conferred by a paternal allele." (Ans. 24.) The Examiner cites no evidence supporting this assertion. In contrast, Rogenhofer teaches that, "[b]ecause M2 carriage has been associated with various thrombophilia-related obstetric complications, it was logical to propose that associated risks would be gender independent, and therefore equally transmitted from each parent." (Rogenhofer 386.) PE, FGR, and RPL are all thrombophilia-related pregnancy pathologies. (*Id.* at 384.)

Accordingly, we reverse the Examiner's rejection of claims 1–5, 7, 17–22, and 24–29 as lacking in enablement.

III.

The Examiner rejects claims 1–5, 7, 17–22, and 24–29 under nonstatutory obviousness-type double patenting as being unpatentable over claims 1–17 of U.S. Patent No. 8,119,341. Appellants have not disputed the merits of this rejection. Accordingly, we summarily affirm the rejection. *See* Manual of Patent Examining Procedure § 1205.02 ("If a ground of rejection stated by the examiner is not addressed in the appellant's brief, that ground of rejection will be summarily sustained by the Board."); *see also In re Berger*, 279 F.3d 975, 984 (Fed. Cir. 2002) (affirming Board's affirmance of an uncontested rejection and finding that the appellant had waived his right to contest the rejection by not presenting arguments as to error in the rejection on appeal to the Board).

SUMMARY

For the reasons above, we affirm the Examiner's rejection of claims 1–5, 7, 17–22, and 24–29 as directed to patent-ineligible subject matter and as being unpatentable under nonstatutory obviousness-type double patenting over claims 1–17 of U.S. Patent No. 8,119,341. We reverse the Examiner's rejection of claims 1–5, 7, 17–22, and 24–29 as lacking in enablement.

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