Trials@uspto.gov
571-272-7822

Paper No. 8
Entered: June 11, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CEPHEID,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC. and
MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH,
Patent Owner.

Case IPR2015-00255
Patent 5,643,723

Before JACQUELINE WRIGHT BONILLA, SUSAN L. C. MITCHELL, and ZHENYU YANG, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

INTRODUCTION

Cepheid ("Petitioner") filed a Petition for an *inter partes* review of claims 1–13 and 17–20 of U.S. Patent No. 5,643,723 ("the '723 patent," Ex. 1001). Paper 1 ("Pet."). Roche Molecular Systems, Incorporated, and Mayo Foundation for Medical Education and Research (collectively, "Patent Owner") timely filed a Preliminary Response. Paper 6 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. *See* 35 U.S.C. § 314(a). Therefore, we deny the Petition for an *inter partes* review.

Related Proceedings

According to the parties, Patent Owner previously asserted the '723 patent against Petitioner in *Roche Molecular Systems, Inc. v. Cepheid*, No. 3:14-cv-03228 (N.D. Cal. filed July 14, 2014). Pet. 1, 2 n.1; Paper 4, 3.

The '723 Patent

The '723 patent "is directed to methods based on the polymerase chain reaction (PCR) for the detection of Mycobacterium tuberculosis (MTB) and concurrent determination of its drug susceptibility, utilizing the appropriate oligonucleotide primers." Ex. 1001, 2:50–54.

MTB causes tuberculosis (TB), a bacterial disease. *Id.* at 1:21–23. Rifampin, an antibiotic, effectively treats TB. *Id.* at 1:31–33. "Rifampin has a unique site of action on the beta subunit (rpoB) of prokaryotic RNA

polymerase." *Id.* at 1:33–34. Mutations conferring rifampin resistance in MTB have been mapped to rpoB. *Id.* at 1:46–60.

At the time of the '723 patent invention, a conclusive diagnosis of TB, which depended on the isolation and identification of MTB, generally required 3–8 weeks. *Id.* at 2:9–11. Such delay contributed to several TB outbreaks. *Id.* at 1:61–2:8. According to the '723 patent, "[a] rapid test that could be performed directly on a patient specimen and that would both confirm a TB diagnosis and indicate whether it is a drug-resistant or drug-sensitive strain would be a major advance." *Id.* at 2:42–46.

The '723 patent discloses a set of "MTB-specific position-specific 'signature nucleotides' that permits unequivocal identification of MTB strains, both drug-resistant and drug-sensitive." *Id.* at 2:63–66. The '723 patent also discloses a PCR-based method for detecting MTB in a biological sample, using primers that hybridize "under hybridizing conditions to a nucleotide sequence containing at least one signature nucleotide" for MTB. *Id.* at 3:50–60.

Illustrative Claims

Claims 1 and 17 are independent claims. Claim 1 is representative. With corrections from the Certification of Correction entered, it reads as follows:

> 1. A method for detecting Mycobacterium tuberculosis in a biological sample suspected of containing M. tuberculosis comprising:
>
> (a) subjecting DNA from the biological sample to polymerase chain reaction using a plurality of primers under reaction

conditions sufficient to amplify a portion of a M. tuberculosis rpoB gene to produce an amplification product, wherein the plurality of primers comprises at least one primer that hybridizes under hybridizing conditions to the amplified portion of the gene at a site comprising at least one position-specific M. tuberculosis signature nucleotide selected, with reference to FIG. 3 (SEQ ID NO:1), from the group consisting:

a G at nucleotide position 2312,
a T at nucleotide position 2313,
an A at nucleotide position 2373,
a G at nucleotide position 2374,
an A at nucleotide position 2378,
a G at nucleotide position 2408,
a T at nucleotide position 2409,
an A at nucleotide position 2426,
a G at nucleotide position 2441,
an A at nucleotide position 2456, and
a T at nucleotide position 2465; and

(b) detecting the presence or absence of an amplification product, wherein the presence of an amplification product is indicative of the presence of M. tuberculosis in the biological sample and wherein the absence of the amplification product is indicative of the absence of M. tuberculosis in the biological sample.

Claim 17 is directed to "[a] primer having 14–50 nucleotides that hybridizes under hybridizing conditions to an M. tuberculosis rpoB gene at a site comprising at least one position-specific M. tuberculosis signature nucleotide selected, with reference to FIG. 3 (SEQ ID NO: 1), from the group consisting of" the eleven signature nucleotides as recited in claim 1.

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims	Basis	Reference(s)
17–19	§ 102(b)	Telenti[1]
1–6, 9–13, 17–20	§ 103	Telenti, Hunt,[2] and Marconi[3]
7, 8	§ 103	Telenti, Hunt, Marconi, and White[4]

In support of its patentability challenge, Petitioner relies on the Declaration of Dr. Richard T. Marconi. Ex. 1026.

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1278–81 (Fed. Cir. 2015).

---

[1] Telenti et al., *Detection of rifampin-resistance mutations in Mycobacterium tuberculosis*, The Lancet 341:647–50 (1993) (Ex. 1002, "Telenti").
[2] Hunt et al., *Detection of a Genetic Locus Encoding Resistance to Rifampin in Mycobacterial Cultures and Clinical Specimens*, Abstracts of the 93rd General Meeting of the American Society for Microbiology, 467, Abstract C-125 (1993) (Ex. 1003, "Hunt").
[3] R.T. Marconi & C.F. Garon, *Development of polymerase chain reaction primer sets for diagnosis of Lyme disease and for species-specific identification of Lyme disease isolates by 16S rRNA signature nucleotide analysis*, J. Clin. Microbiol. 30:2830–34 (1992) (Ex. 1004, "Marconi").
[4] T.J. White & D.E. Dodge, Int'l Pub. No. WO 91/14002, published on September 19, 1991 (Ex. 1006, "White").

Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Petitioner proposes that we construe the terms "hybridizes under hybridizing conditions" and "is indicative of." Pet. 17–19. Patent Owner disagrees with Petitioner's proposed constructions for these terms. Prelim. Resp. 5–10. In addition, Patent Owner asks us to construe "primer" and "amplification product." *Id.* at 10–14. We address each term in turn.

<u>"Hybridizing Conditions"</u>

Claims 1 and 17 recite a primer that "hybridizes under hybridizing conditions." Petitioner argues that "hybridizing conditions" include all those discussed in the '723 patent, such as "hybridization at 55° C (a PCR reaction) and 42° C (a hybridization assay)." Pet. 17 (citing Ex. 1001, 10:33–54, 18:19). In addition, the Specification discloses that the "hybridizing and amplification conditions used in the present invention include an annealing temperature of about 60°–75° C." *Id.* (quoting Ex. 1001, 4:40–49). Petitioner also points to the Specification where it discloses using 50 mM KCl, 1.5 mM $MgCl_2$, pH 8.3 buffer, and 10% glycerol in some PCR reactions. *Id.* (citing Ex. 1001, 16:57–61). Therefore, according to Petitioner, "hybridizing conditions should be construed to include (without necessarily being limited to) an annealing temperature of

42–75º C in the presence of 5–15% glycerol by volume, about 50 mM KCl, and about 1.5 mM $MgCl_2$." *Id.* at 17–18.

Patent Owner contends that both claim 1 and the Specification use the term "primer" only in connection with its use in a PCR reaction. Prelim. Resp. 5–6 (citing Ex. 1001, 3:2–9, 3:50–60, 6:17–20); *see also* Ex. 1001, claim 1 (reciting "subjecting DNA . . . to polymerase chain reaction using . . . at least one primer that hybridizes under hybridizing conditions"). Thus, according to Patent Owner, the "hybridizing conditions" recited in claims 1 and 17 "must refer to PCR conditions, and, more specifically, to the hybridization, or annealing, step" in relation to the recited primer. *Id.* at 6 (citing Ex. 1026 ¶ 22). We agree with Patent Owner.

Petitioner refers to the Specification where it states "[h]ybridization conditions (42° C., 16 hours)." Pet. 17 (citing Ex. 1001, 18:19). Petitioner's reliance on this single sentence is misplaced. As Patent Owner correctly points out, this sentence appears in a passage that describes a Southern blot analysis, which "does not utilize a primer, and is unrelated to PCR." Prelim. Resp. 6 (citing Ex. 1001, 18:10–22). Petitioner does not argue or establish sufficiently that the disclosed conditions for preforming Southern blot analysis would have informed an ordinary artisan of appropriate conditions for hybridizing a primer in the recited PCR. Based on the record before us, because claims 1 and 17 only concern PCR reactions, the hybridization conditions recited therein do not encompass the 42° C hybridization temperature for Southern blot analysis.

After considering the entirety of the '723 patent, we determine that, under the broadest reasonable construction consistent with the Specification,

"hybridizing conditions" means "the conditions under which a primer hybridizes to the target DNA during the PCR annealing step."

"Is Indicative of"

Petitioner proposes:

> [The term] "is indicative of" should be construed to reflect a one-to-one correspondence—i.e., the presence of an amplification product occurs only if MTB is present in the sample, and the absence of an amplification product occurs only if MTB is absent from the sample, because only *rpoB* from MTB is amplified.

Pet. 18–19. Patent Owner disagrees. Prelim. Resp. 8–10. We determine that, for purposes of this Decision, it is unnecessary to expressly construe the term.

"Primer" and "Amplification Product"

Patent Owner proposes that we construe the terms "primer" and "amplification product." Prelim. Resp. 10–14.

Petitioner does not propose explicitly any construction for either term. Nevertheless, citing the Declaration of Dr. Marconi and relying on U.S. Patent No. 4,683,202 ("the '202 patent," Ex. 1009), issued in 1987, it contends that a primer is "an oligonucleotide that is capable of being extended by a polymerase." Pet. 21 (citing Ex. 1026 ¶ 26, Ex. 1009, 4:24–32).

Patent Owner characterizes this definition as "unreasonably broad." Prelim. Resp. 11–12. According to Patent Owner, "there is an art recognized distinction" between these two terms, i.e., "a primer is used to

initiate amplification and produce an amplification product." *Id.* at 10. Patent Owner proposes that a "primer" is "a single-stranded oligonucleotide that can be extended during PCR amplification to form an amplification product," and an "amplification product" is "an oligonucleotide produced via extension of a primer during PCR amplification." *Id.* at 14.

To support its argument, Patent Owner first relies on the '723 patent. Prelim. Resp. 12–13. According to Patent Owner, the claims and the Specification make it clear that primers are single stranded oligonucleotides that initiate PCR amplification reactions. *Id.*

Patent Owner also refers to the '202 patent, the exhibit relied on by Petitioner. *Id.* The '202 patent states that a primer "is capable of acting as a point of initiation of synthesis when placed under conditions in which synthesis of a primer extension product which is complementary to a nucleic acid strand is induced." Ex. 1009, 4:24–32. It also discloses that a primer is preferably single stranded. *Id.* at 4:33. A double stranded primer, although possible, must be first "treated to separate its strands before being used to prepare extension products." *Id.* at 4:34–37.

Patent Owner further points to the Declaration of Dr. Marconi, Petitioner's witness. Prelim. Resp. 12, 13. According to Dr. Marconi, a primer is a short strand of DNA that hybridizes to the opposite strand of a specific target DNA at a specific site. Ex. 1026 ¶ 20. He explains the three steps of a PCR reaction: (1) denaturation where double stranded DNA is separated into single strands; (2) hybridization where primers hybridize to target DNA in a sample; and (3) extension where "DNA polymerase added

nucleotides one at a time to the 3' end of hybridized primers" to form amplification products. *Id.* ¶¶ 21–23.

Based on the current record, we agree with Patent Owner that a "primer" is different from an "amplification product" in that a primer is a single stranded oligonucleotide used to initiate the amplification in a PCR reaction, whereas an amplification product is the result of the primer extension.

Patentability Analysis

Anticipation by Telenti

Petitioner asserts that Telenti inherently anticipates claims 17–19. Pet. 19–25. Based on the current record, we determine that Petitioner has not established a reasonable likelihood it would prevail in this assertion.

Telenti reports the identification of rifampicin-resistant mutations in MTB.[5] Ex. 1002, 647. Specifically, using two primers TR1 and TR2b, Telenti amplified a highly conserved rpoB fragment of MTB. *Id.* at 648. The sequence of the fragment was submitted to GenBank and assigned the accession number L05910. *Id.*, *see also* Ex. 1005 (showing the sequence of GenBank L05910 and variations conferring rifampin resistance). According to Telenti, the sites of rifampicin-resistant rpoB mutations correspond to amino acids highly "conserved between *M tuberculosis* and *M leprae* (EMBL databank Z14314)" and several other bacterial species. Ex. 1002,

[5] According to Dr. Marconi, rifampicin is synonymous to rifampin. Ex. 1026 ¶ 27.

647, 649, *see also* Ex. 1012 (showing the sequence of EMBL Z14314). Mutations of these amino acids also "result[] in rifampicin resistance in *E. coli*." Ex. 1002, 649. In addition, Telenti discloses PCR-single-strand conformation polymorphism for rapid detection of rifampicin resistance in MTB. *Id.* To do so, Telenti used two other primers, TR8 and TR9. *Id.* at 648.

Petitioner acknowledges that Telenti does not "expressly state that any of its primers hybridized to a site comprising at least one of the listed signature nucleotides" recited in claim 17. Pet. 54. Nevertheless, Petitioner points to TR8, one of the primers disclosed in Telenti. *Id.* at 22. According to Petitioner,

> The TR8 sequence is a perfect complement . . . of positions 2473–2491 of the *rpoB* sequence in Fig. 3A of the '723 patent, as illustrated below:
>
> TGCCGGGCTGGAGGTCCGCGACGTGCA-3' (2465-2491 in Fig. 3A)
> ||||||||||||||||||||
> 3'-ACCTCCAGGCGCTGCACGT-5' (TR8)

Id. at 22–23 (internal citation omitted). The shaded T at position 2465 (in the sequence presented in Figure 3A of the '723 patent) is one of the signature nucleotides recited in claim 17. *Id.* at 23.

Using TR8 and TR9 as the primers and rpoB fragment of MTB as the template, Telenti discloses, a PCR reaction would generate a 157 bp product. Ex. 1002, 648. Petitioner argues that in this reaction, "*[i]f* a primer in a PCR reaction produces the correct amplification product, the primer necessarily is extended one base at a time by DNA polymerase, and each added base is complementary to the target sequence being amplified." Pet. 23 (emphasis

added). And, according to Petitioner, when the rpoB fragment from rifampin-sensitive MTB is the template,

> A 27-base oligonucleotide with the sequence TGCACGTCGCGGACCTCCAGCCCGGCA was briefly but necessarily produced during the extension reaction after eight nucleotides had been added, as shown below.
>
> ```
> TGCCGGGCTGGAGGTCCGCGACGTGCA-3' (2465-2491, Fig. 3A)
> |||||||||||||||||||||||||||
> 3'-ACGGCCCGACCTCCAGGCGCTGCACGT-5' (TR8 extended by 8 nt)
> ```

Pet. 23 (internal citation omitted). This 27-base oligonucleotide, Petitioner asserts, anticipates claim 17. *Id.* at 23–24. We are not persuaded.

Petitioner relies on an inherency theory to support its anticipation argument. Pet. 19–24. Under the inherency doctrine, a prior art reference may anticipate without expressly disclosing a claimed limitation "if that missing characteristic is *necessarily* present in the single anticipating reference." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (emphasis added). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co. USA, Inc., v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991).

Telenti performed the PCR reactions using *Taq* polymerase. Ex. 1002, 648. Patent Owner argues that because *Taq* polymerase was known to have low fidelity, it was "not guaranteed to incorporate the correct

base each and every time." Prelim. Resp. 18 (citing Ex. 2001,[6] 9253). As a result, according to Patent Owner, Petitioner can demonstrate that the "correct amplification product" is generated only most of the time, but not all the time. *Id.* Thus, Patent Owner contends, Petitioner "has failed to meet the high threshold required to show inherent anticipation." *Id.* We agree.

Evidence indicates that *Taq* polymerase has a high error rate that "would create serious background problems" when using PCR to study point mutations. Ex. 2001, 9253. Indeed, the error rate for *Taq* polymerase in PCR is 2×10^{-4} per base duplication, which would result in an accumulation of 0.8 mutant position after 20 duplications of a 100-bp sequence. *Id.* In Telenti, the PCR reaction using TR8 as a primer "was subjected to 40 cycles of amplification" and the expected product is 157 bp. Ex. 1002, 648. That reaction, statistically, would accumulate more than one mutation in the amplified product. As a result, the 27-bp oligonucleotide with the sequence TGCACGTCGCGGACCTCCAGCCCGGCA, contrary to Petitioner's assertion, was not necessarily produced.

In addition, as Petitioner acknowledges, "when it was formed, the [27-bp] oligonucleotide was hybridized under hybridizing conditions to an MTB *rpoB* DNA." Pet. 24. In other words, any 27-bp oligonucleotide that Telenti might have produced would not have been single stranded, as a primer must be under our claim construction, but rather would have been formed as a double stranded amplification product.

---

[6] P. Keohavong & W.G. Thilly, *Fidelity of DNA polymerases in DNA amplification*, Proc. Natl. Acad. Sci. USA, 86: 9253–57 (1989) (Ex. 2001).

For the reasons explained above, we conclude that Petitioner has not established a reasonable likelihood it would prevail in showing that Telenti inherently anticipates claim 17. Claim 18 depends from claim 17, and claim 19 depends from claim 18. Because a dependent claim incorporates by reference all the limitations of the claim to which it refers, we similarly conclude that Petitioner has not established a reasonable likelihood it would prevail in showing that Telenti inherently anticipates claims 18 and 19.

Obviousness over Telenti, Hunt, and Marconi

Petitioner asserts that claims 1–6, 9–13, and 17–20[7] would have been obvious over Telenti, including the sequences disclosed as L05910 and Z14314, in view of Hunt and Marconi. Pet. 25–57. Based on the current record, we determine that Petitioner has not established a reasonable likelihood it would prevail in this assertion.

Claims 1–6 and 9–13

Petitioner argues that Telenti teaches "subjecting DNA from a biological sample to polymerase chain reaction using a plurality of primers under reaction conditions sufficient to amplify a portion of a *M. tuberculosis rpoB* gene to produce an amplification product." Pet. 28. In addition,

[7] The heading for Section VIII.B, as it appears in both Table of Contents and in the body of the Petition, does not mention claims 17–20. Pet. ii, 25. We note, however, claims 17–20 are included in the Statutory Grounds of Challenge section. *Id.* at 3. Further, Petitioner provides obviousness analyses of claims 17–20. *Id.* at 12, 54–57.

Telenti teaches "detecting the presence or absence of an amplification product." *Id.* at 28–29. Petitioner acknowledges that "Telenti did not expressly mention that the method achieved species-specific amplification using a primer that hybridized at a site comprising at least one position-specific M. tuberculosis signature nucleotide selected from one of the eleven listed in claim 1." *Id.* at 29. Petitioner asserts, however, "one of ordinary skill would have been motivated to modify Telenti's method to do so and would have expected the modified method to succeed." *Id.* We are not persuaded.

We take "an expansive and flexible approach" in our obviousness inquiry. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 415 (2007). Nevertheless, a conclusion of obviousness "cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* at 418. Specifically, it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field" to modify or to combine prior art teachings to arrive at the claimed invention. *Id.* at 418–19. Petitioner falls short in at least this requirement in its obviousness challenge.

Specifically, Petitioner observes Telenti's statement that the study therein "represents a first step towards development of rapid detection methods for drug-resistant *M tuberculosis*." Pet. 29 (quoting Ex. 1002, 650). From this sentence, Petitioner concludes that "one of ordinary skill would have wanted to identify the resistant bacterium in the sample as MTB in addition to detecting rifampin resistance." *Id.* at 29–30 (citing Ex. 1026

¶¶ 45–46). We disagree. In Telenti, all the samples evaluated were known clinical isolates of MTB from TB patients. Ex. 1002, 647, 648. It, thus, was unnecessary to identify the bacterium as MTB. Instead, Telenti was solely concerned with identifying rifampicin-resistant mutations in MTB. *Id.* at 647–50. Nowhere does Telenti mention any need to identify, or suggest any interest in identifying, species-specific signature nucleotides in MTB.

Petitioner cites two paragraphs in the Declaration of Dr. Marconi as support. Pet. 29–30 (citing Ex. 1026 ¶¶ 45–46). Those paragraphs, however, merely parrot the argument presented in the Petition. *Compare* Pet. 29–30 *with* Ex. 1026 ¶¶ 45–46. They also are unsupported by sufficient evidence. For example, during prosecution, Patent Owner's attorney "stated that Telenti's primers would produce amplification product from the *rpoB* genes of bacteria other than MTB, because the *rpoB* gene was known to be highly conserved." Ex. 1026 ¶ 46, Ex. 1020, 13. Dr. Marconi acknowledges this statement but testifies, without any explanation, that "one of ordinary skill would have been motivated to modify Telenti's method to provide species-specific amplification to rapidly identify MTB." Ex. 1026 ¶ 46. Dr. Marconi does not reconcile this conclusion with Telenti, which repeatedly emphasizes that both the *rpoB* fragment studied and the rifampicin-resistant mutations are highly conserved across species. *See* Ex. 1002, 648–50.

Petitioner next argues that "one of ordinary skill would have been motivated to improve Telenti's method by identifying MTB at the amplification stage using species-specific primers," "[e]specially in view of

Hunt's disclosure of expected sequence variation amongst related bacteria in the [rifampin resistance] region of" rpoB. Pet. 31. We are not persuaded.

Hunt teaches using PCR to detect a rifampin-resistant gene as a surrogate test for drug-resistant TB in clinical specimens. Ex. 1003, C-125. It used degenerate primers "designed based on highly conserved regions" of rpoB to amplify a region that "contains most mutations conferring rifampin resistance in TB." *Id.* According to Hunt, a PCR product of expected size "was amplified from rifampin-sensitive and -resistant TB isolates." *Id.* Hunt also used primers derived from TB rpoB fragment to amplify DNA from several other bacterial and mycobacterial isolates. *Id.*

Conceding that "Hunt's primers were not species-specific," Petitioner nevertheless asserts that "one of ordinary skill would have expected that sequence variation occurring in and around the rifampin resistance region of *rpoB* could be used to distinguish MTB from related bacteria." *Id.* at 31. Citing Dr. Marconi's Declaration, Petitioner emphasizes a statement in Hunt that "[a]utomated sequence analysis of the amplified product . . . will provide additional specificity and a rapid method for detecting rifampin-resistant TB." *Id*. (citing Ex. 1026 ¶ 48 (quoting Ex. 1003)). According to Dr. Marconi,

> A person of ordinary skill would have understood that this meant that although the PCR amplification described in Hunt was not species-specific for MTB, the sequence of the *rpoB* gene of MTB included differences from the *rpoB* of other bacteria, and that these differences could be used to develop "a rapid method for detecting rifampin-resistant TB" that would distinguish MTB DNA from DNA of other bacteria.

Ex. 1026 ¶ 48.

Patent Owner offers a different reading of the same sentence. According to Patent Owner, "the 'additional specificity' referred to in that sentence is rifampicin resistance specificity," and not species specificity. Prelim. Resp. 30. We find Patent Owner's argument more persuasive. The degenerate primers in Hunt amplified the rpoB region "from rifampin-sensitive and -resistant TB isolates." Ex. 1003, C-125. As Patent Owner points out, this "is not sufficiently specific to determine if a given isolate is actually rifampin resistant." Prelim. Resp. 24. Given that Hunt set out to detect the "Genetic Locus Encoding Resistance to Rifampin in Mycobacterial Cultures and in Clinical Specimens" (Ex. 1003, C-125), we agree with Patent Owner that "the logical interpretation of the sentence [mentioning 'additional specificity'] from the context of the entire Hunt reference is that sequence analysis will be used to detect the presence of the rifampin resistance mutations." Prelim. Resp. 29–30.

Finding inadequate support, we reject Petitioner's contention that "one of ordinary skill would have expected the existence of signature nucleotides in areas flanking the MTB *rpoB* segment containing the rifampin resistance mutations." *See* Pet. 34. Thus, we determine that, contrary to Petitioner's position, evidence before us does not establish sufficiently that one of ordinary skill would have been motivated to modify Telenti's method of detecting rifampin-resistance mutations into one of identifying MTB through signature nucleotides in MTB rpoB.

Furthermore, we determine that Petitioner has not explained adequately why one of ordinary skill would have combined the teachings of Marconi with those of Telenti and Hunt. Marconi does not relate to MTB or

the rpoB gene. Instead, it teaches species-specific identification of the bacteria that cause Lyme disease. Ex. 1004, Abstract. Specifically, Marconi determined and aligned partial 16S rRNA sequences from about two-dozen Lyme disease isolates to identify signature nucleotides. *Id.*, *id.* at 2831. It then used the signature nucleotides unique to each species to develop species-specific PCR primers. *Id.* at 2832.

Petitioner contends that the methods in Marconi "were not limited to the particular gene or organisms that were used." Pet. 33. Instead, according to Petitioner, highly conserved genes are attractive targets for both diagnosis and species-specific identification. *Id.* at 33–34 (citing Ex. 1026 ¶ 56). Because both Telenti and Hunt describe the rpoB region as "highly conserved," Petitioner reasons, rpoB "would have been recognized as an attractive target for Marconi's species-specific amplification method." *Id.* at 34 (citing Ex. 1026 ¶ 57). We are not persuaded.

For purposes of this Decision, we assume, without deciding, as Petitioner asserts, highly conserved genes are attractive targets for species-specific identification. Petitioner, however, does not argue that rpoB is the only, or even one of a finite number of conserved genes in MTB. Petitioner does not offer any persuasive evidence to show why one of ordinary skill in the art would have chosen rpoB, instead of any other conserved genes, to develop a method for species-specific identification. *See Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008) (even post-*KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention").

In sum, we are not persuaded that Petitioner has explained adequately why an ordinary artisan would have considered it obvious to modify the method of Telenti (and Hunt) for detecting rifampin-resistant mutations in MTB, with the teachings of Marconi, to develop a method for species-specific identification, as recited in claim 1. Thus, we conclude that Petitioner has not established a reasonable likelihood it would prevail in showing that claim 1 would have been obvious over Telenti, Hunt, and Marconi. Because claims 2–6 and 9–13 depend directly or indirectly from claim 1, we similarly conclude that Petitioner has not established a reasonable likelihood it would prevail in showing that claims 2–6 and 9–13 would have been obvious over Telenti, Hunt, and Marconi.

Claims 17–20

Claims 17–20 are directed to a primer that hybridizes under hybridizing conditions to an MTB rpoB gene at a site comprising at least one of eleven position-specific MTB signature nucleotides. Petitioner acknowledges that none of the asserted references expressly discloses any of the claimed primers. Pet. 54. Petitioner, however, argues that the claimed primers would have been obvious over the teachings of Telenti, Hunt, and Marconi. *Id.* Based on the current record, we determine that Petitioner has not established a reasonable likelihood it would prevail in this assertion.

Petitioner relies on the same rationale as discussed for claim 1. *Id.* at 54–55. According to Petitioner, a skilled artisan would have had a reason to modify Telenti's method in view of Hunt and Marconi, would have used Marconi's methods to identify signature nucleotides in MTB rpoB, and

would have applied Marconi's teaching to design species-specific primers for MTB rpoB as recited in claim 17. *Id.*

As explained above, Petitioner does not point to either the cited prior art or general knowledge in the field for teaching or suggesting any correlation between rifampin-resistant mutations and species-specific signature nucleotides in MTB rpoB. Thus, we are not persuaded that Petitioner has explained adequately why an ordinary artisan would have considered it obvious to modify the method of Telenti (and Hunt) for detecting rifampin-resistant mutations in MTB, with the teachings of Marconi, to develop a primer for species-specific identification, as recited in claim 17.

We, therefore, conclude that Petitioner has not established a reasonable likelihood it would prevail in showing that claim 17 would have been obvious in view of Telenti, Hunt, and Marconi. Because claims 18–20 depend directly or indirectly from claim 17, we similarly conclude that Petitioner has not established a reasonable likelihood it would prevail in showing that claims 18–20 would have been obvious over Telenti, Hunt, and Marconi.

<u>Obviousness over Telenti, Hunt, Marconi, and White</u>

Petitioner asserts that claims 7 and 8 would have been obvious over Telenti, including the sequences disclosed as L05910 and Z14314, in view of Hunt, Marconi, and White. Pet. 58–59. Based on the current record, we determine that Petitioner has not established a reasonable likelihood it would prevail in this assertion.

Claim 7 depends independently from claim 1. It requires that the PCR comprises "a hemi-nested polymerase chain reaction." Claim 8 depends from claim 7 and further requires that "the plurality of primers comprises at least three different primers." Petitioner argues that White teaches both additional limitations. *Id.* at 58–59. Petitioner does not rely on White to remedy the deficiency of Telenti, Hunt, and Marconi, as discussed above. As a result, we conclude that, for the same reasons explained above in discussing the obviousness challenge of claim 1, Petitioner has not established a reasonable likelihood it would prevail in showing that claims 7 and 8 would have been obvious in view of Telenti, Hunt, Marconi, and White.

CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence does not establish a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 1–13 and 17–20 of the '723 patent.

ORDER

Accordingly, it is

ORDERED that Petitioner's request for an *inter partes* review of claims 1–13 and 17–20 of the '723 patent is *denied*.

PETITIONER:

M. Paul Barker
Erik R. Puknys
Adam M. Breier
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
paul.barker@finnegan.com
erik.puknys@finnegan.com
adam.breier@finnegan.com

PATENT OWNER:

R. Danny Huntington
Seth E. Cockrum
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
dhuntington@rfem.com
scockrum@rfem.com