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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte RACHEL LANGLAND, LIN WU, THAD SHARP, and
STEPHEN WILL¹

Appeal 2015-004842
Application 13/015,374
Technology Center 1600

Before ERIC B. GRIMES, RICHARD J. SMITH, and RYAN H. FLAX,
Administrative Patent Judges.

SMITH, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of determining sensitivity of cancer cells to a BRAF kinase inhibitor. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

¹ According to Appellants, the real party in interest is ROCHE MOLECULAR SYSTEMS, INC. (Br. 5.)

STATEMENT OF THE CASE

Background

“The invention provides a diagnostic assay to detect a mutation at position 600 of the *BRAF* gene for use in selecting cancer patients . . . who are candidates for treatment with a B-Raf inhibitor.” (Spec. ¶ 31.)

Claims on Appeal

Claims 1 and 5–24 are on appeal.² (Appendix, Br. 23–26.) Claim 1, the only independent claim, is illustrative and reads as follows:

1. A method of determining sensitivity of cancer cells to a BRAF kinase inhibitor, the method comprising: providing a nucleic acid sample from cancer cells from a patient that has a cancer; amplifying a target polynucleotide sequence in the nucleic acid sample using a primer pair that amplifies the target polynucleotide sequence, wherein the target polynucleotide sequence comprises codon 600 in BRAF and amplification is performed in the presence of a labeled oligonucleotide probe that consists of SEQ ID NO:1 and detects the presence of a mutated sequence at the codon 600 in BRAF consisting of the mutations V600E, V600D and V600K; and detecting the presence or absence of a mutation V600E, V600D or V600K in BRAF; determining that the cancer is sensitive to the BRAF inhibitor if the mutation V600E, V600D or V600K in BRAF is present.

(Br. 23.)

Examiner’s Rejections

1. Claims 1, 5–14, 17–19, and 21 stand rejected under 35 U.S.C.

² Claims 25–32 are withdrawn from further consideration as being drawn to a nonelected invention. (Final Act. dated May 29, 2014, at 2.)

§ 103(a) as unpatentable over Mitsiades,³ Benlloch,⁴ Kinoshita,⁵ Spittle,⁶ and GenBank.⁷ (Final Act. 10.)

Claims 1, 5–14, 17–19, and 21 were not argued separately, and we therefore limit our consideration to claim 1.

2. Claim 15 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Mitsiades, Benlloch, Kinoshita, Spittle, GenBank, and Syvänen.⁸ (*Id.* 19.)

3. Claim 16 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Mitsiades, Benlloch, Kinoshita, Spittle, GenBank, and Bustin.⁹ (*Id.* 20–21.)

4. Claim 20 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Mitsiades, Benlloch, Kinoshita, Spittle, GenBank, and Chen.¹⁰ (*Id.* 21.)

³ Mitsiades et al., *Targeting BRAF^{V600E} in thyroid carcinoma: therapeutic implications*, MOL. CANCER THER. 6(3), 1070–78 (2007) (“Mitsiades”).

⁴ Benlloch et al., *Detection of BRAF V600E Mutation in Colorectal Cancer Comparison of Automatic Sequencing and Real-Time Chemistry Methodology*, 8 J. MOL. DIAGN. 5, 540–43 (2006) (“Benlloch”).

⁵ Kinoshita et al., *Application of probes having 2'-deoxyinosine for typing of single nucleotide polymorphisms (SNPs) using DNA microarray*, ANALYTICA CHIMICA. ACTA. 561, 25–31 (2006) (“Kinoshita”).

⁶ Spittle et al., *Application of a BRAF Pyrosequencing Assay for Mutation Detection and Copy Number Analysis in Malignant Melanoma*, 9 J. MOL. DIAGN. 4, 464–71 (2007) (“Spittle”).

⁷ GenBank Accession NM_004333.3 GI: 90265828 (Aug. 20, 2006) (“GenBank”).

⁸ Syvänen, *Assessing Genetic Variation: Genotyping Single Nucleotide Polymorphisms*, 2 NATURE REV. 930–42 (2001) (“Syvänen”).

⁹ Bustin, *Absolute quantification of mRNA using real-time reverse transcription polymerase chain reaction assays*, 25 J. MOLECULAR ENDOCRINOLOGY, 169–93 (2000) (“Bustin”).

¹⁰ Chen et al., US 2002/0150925 A1, published Oct. 17, 2002 (“Chen”).

5. Claim 22 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Mitsiades, Benlloch, Kinoshita, Spittle, GenBank, and Tsai.¹¹ (*Id.* 22–23.)
6. Claim 23 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Mitsiades, Benlloch, Kinoshita, Spittle, GenBank, and Sidransky.¹² (*Id.* 23–24.)
7. Claim 24 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Mitsiades, Benlloch, Kinoshita, Spittle, GenBank, Sidransky, and Tsai. (*Id.* 25.)

ISSUE

Whether a preponderance of the evidence of record supports the Examiner’s conclusions of obviousness under 35 U.S.C. § 103(a).

Rejection No. 1

Analysis

The Examiner concludes that, based on the cited art, claim 1 would have been obvious to one of ordinary skill in the art at the time of the invention. (Final Act. 10–19.) Appellants’ rebuttal focuses on objective evidence of nonobviousness, and includes the Cheng Declaration¹³ and Sharma Affidavit.¹⁴ (Br. 15–22.)

¹¹ Tsai et al., *Development of a novel inhibitor of cogenic b-raf*, 47 Proc. Amer. Assoc. Cancer Res., Abstract (2006) (“Tsai”).

¹² Sidransky et al., US 2005/0048533 A1, published Mar. 3, 2005 (“Sidransky”).

¹³ Declaration under 37 CFR 1.132 Submitted with Response to an Office Action, by Suzanne Cheng, dated Feb. 11, 2014 (“Cheng Declaration” or “Decl.”).

¹⁴ Affidavit under 37 CFR 1.132 Submitted with Response to an Office Action, by Ashish Sharma, dated Oct. 18, 2012 (“Sharma Affidavit” or

We adopt the Examiner’s findings and analysis as set forth in the Final Action (Final Act. 10–35) and Answer (Ans. 2–11). Moreover, for the reasons set forth therein, and for the reasons set forth below, we conclude that the Examiner has established a prima facie case of obviousness and that Appellants’ arguments and evidence do not overcome or rebut that prima facie case.

Unexpected Results

Appellants state that “[t]he method utilizes a probe (SEQ ID NO: 1) that was designed to detect the most common mutation V600E. Unexpectedly, the probe was also able to detect rare mutations V600D and V600K.”¹⁵ (Br. 11.) Appellants point to the Cheng Declaration, that quotes an article by Anderson,¹⁶ to argue that “Dr. Cheng explains why detection of the V600K mutation was considered unexpected.” (*Id.* at 17, citing Cheng Decl. ¶ 5.) Appellants also point to the Cheng Declaration, and an article by Chapman,¹⁷ to argue that “finding that V600K tumors also respond to the

“Aff.”). The Sharma Affidavit generally relates to sales of the cobas[®] kit which “enables a user to practice the method described in claim 1 of the patent application.” (Aff. ¶ 4.)

¹⁵ We note that claim 1 recites that SEQ ID NO:1 “detects the presence of a mutated sequence at the codon 600 in BRAF consisting of the mutations V600E, V600D and V600K.” (Br. 23, emphasis added.)

¹⁶ Anderson et al., *Multisite Analytic Performance Studies of a Real-Time Polymerase Chain Reaction Assay for the Detection of BRAF V600E Mutations in Formalin-Fixed Paraffin-Embedded Tissue Specimens of Malignant Melanoma*, 136 ARCH. PATHOL. LAB. MED. 1–7 (2012) (“Anderson”).

¹⁷ Chapman et al., *Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation*, 364 N. ENGL. J. MED. 2507–2516 (2011) (“Chapman”).

BRAF V600E-specific inhibitor vemurafenib was an unexpected result with a significant practical advantage.” (*Id.* at 17–18, citing Cheng Decl. ¶ 6.) Based on these arguments, Appellants contend that the Examiner erred in relying on Kinoshita (n.5 *supra*) to conclude that “the ability of SEQ ID NO:1 to bind all three of the mutations V600E, V600D and V600K . . . is not unexpected,” because “Kinoshita offers no more than general guidance on using inosine in probes.” (*Id.* at 18–19.)

Unexpected results require a showing that a person of ordinary skill in the art would have found the results (i.e., detecting V600D and V600K mutations) unexpected. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Moreover, for the reasons set forth in the Answer and as discussed below, we agree with the Examiner that the results proffered by Appellants are not shown to be unexpected, and find no error in the Examiner’s reliance on Kinoshita.

The Cheng Declaration quotes Anderson as stating:

The cobas test while not specifically designed for the detection of non-V600E mutations, demonstrated substantial cross-reactivity with some non-V600E mutations and this detected 70% of V600K mutations and the only V600D-mutation [sic] in this cohort. (p. 5, right col., 1st par., emphasis added.)

(Decl. ¶ 5.)

The complete quote, with deleted wording included in italics, reads as follows:

The cobas test, while not specifically designed for the detection of non-V600E mutations *or being able to discriminate between codon 600 mutations*, demonstrated substantial cross-reactivity with some non-V600E mutations, and thus detected 70% of the V600K mutations and the only V600D-mutation in this cohort.

(Anderson 5, rt. col., ll. 6–11, emphasis added.)

We are not persuaded that the above quote shows that a person of ordinary skill in the art would have found the detection of mutations at codon 600 other than V600E mutations by Appellants' probe to be unexpected. Moreover, we do not find any reason to conclude that the detection of V600D and V600K mutations would have been unexpected, based on an accurate quote of Anderson, because Appellants' test was not specifically designed for *being able to discriminate between codon 600 mutations*. (*Id.*) That is, it appears that the complete statement from Anderson reflects that, while Appellants' test was “not specifically designed for the detection of non-V600E mutations,” it was understood that non-V600E mutations would be detected, albeit without discriminating between the particular mutations at codon 600. The complete statement thus suggests that it was not unexpected that Appellants' probe would detect mutations other than V600E, such as V600K or V600D. Moreover, Appellants' argument regarding Chapman and the “practical advantage” of detecting V600K mutations is similarly unpersuasive of unexpected results.

State of Prior Art

Appellants refer to the Cheng Declaration, and its citation to Chapman, to argue that “the art did not recognize the need to test for the V600K mutation as it was not known that the V600E-specific drug could benefit those patients as well.” (Br. 19–20, citing Cheng Decl. ¶ 6.)

Appellants also refer to the Cheng Declaration to argue the “inability of prior art to solve the problem.” (*Id.* at 20–21, citing Cheng Decl. ¶¶ 8–11.)¹⁸

The Examiner explains that the prior art of Spittle (n.6 *supra*) teaches “that [it] is important to use an assay that identifies the common V600E as well as variant BRAF mutations” and that Spittle discloses “a pyrosequencing assay that was able to detect the V600E, V600K, V600D, and V600R mutations.” (Ans. 8.) We are thus not persuaded that the prior art did not (1) recognize the need to test for the V600K mutation, or (2) solve the alleged problem of detecting the V600K mutation.

Praise by Others

Appellants point to the Cheng Declaration and several articles cited therein as allegedly “praising the unique ability of the method to detect additional mutations, especially V600K.” (Br. 20, citing Cheng Decl. ¶ 7.) However, our review of the cited articles indicates that, at most, Appellants’ test was more (or less) sensitive compared to other similar tests, but that the articles do not reflect any “unique” ability of the claimed method to detect additional mutations. (*See also* Ans. 9.)

Commercial Success

Appellants point to the Sharma Affidavit to argue “successful sales of the product incorporating the invention despite the availability of less expensive similar tests.” (Br. 21.) The Sharma Affidavit refers to a BRAF Sell Sheet (Exhibit 1) and a Product Insert (Exhibit 2) as referring to the

¹⁸ The Cheng Declaration cites to articles and other documents. (Cheng Decl. ¶¶ 8–11.)

sensitivity of the cobas[®] kit towards V600 mutations other than V600E.
(Aff. ¶¶ 5, 6.)

The Sharma Affidavit addresses sales of the cobas[®] kit by stating that while “the use of the cobas[®] kit is not *required* to detect the BRAF mutations,” the cobas[®] kit “has been continuously displacing cheaper” lab developed tests despite its higher cost. (*Id.* ¶ 7.) This statement is supported by a chart (Exhibit 3) identified as showing “the share of the testing market in the U.S. for each test since the introduction of the cobas[®] kit.” (*Id.*) The Sharma Affidavit also states that “[i]n my opinion, the sales of the cobas[®] kit have been excellent in the United States and good in the rest of the world,” including a chart (Exhibit 4) listing numbers of sales by country. (*Id.* ¶¶ 8, 9.) Furthermore, according to the Sharma Affidavit, while “[m]any factors may have contributed to excellent sales of the cobas[®] kit . . . sensitivity, specificity, and unique mutation detection profile . . . are definitely among the contributing factors.” (*Id.* ¶ 10.)

In the *ex parte* process of patent examination, the USPTO “must rely upon the applicant to provide hard evidence of commercial success.” *In re Huang*, 100 F.3d 135, 139–40 (Fed. Cir. 1996) (noting that the USPTO “lacks the means or resources to gather evidence which supports or refutes the applicant’s assertion that the sales constitute commercial success”). We find such hard evidence lacking in the present case, and that Appellants have failed to persuasively establish either commercial success or a nexus between sales and the claimed method.

While Appellants provide data regarding the number of cobas[®] kits sold, “evidence related solely to the number of units sold provides a very weak showing of commercial success, if any.” *Huang*, 100 F.3d at 140

(citing cases). In this case, Appellants' sales data "provides no indication of whether this represents a substantial quantity in this market." *Id.* Thus, Appellants have failed to provide sufficient information to determine whether the cobas[®] kit has been commercially successful. *See id.*

Even if Appellants had established commercial success, that success would only be relevant "if there is proof that the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *Id.* The Sharma Affidavit indicates that many factors may have contributed to sales and that the "unique mutation detection profile" is "definitely among the contributing factors." (*Id.* ¶ 10.) Such conclusory assertions do not establish the required nexus between the sales and claimed invention, such as might be achieved by "an affidavit from the purchaser explaining that the product was purchased due to the claimed features." *See Huang*, 100 F.3d at 140.

Conclusion of Law

A preponderance of the evidence of record supports the Examiner's conclusion that claim 1 is obvious under 35 U.S.C. § 103(a). Furthermore, Appellants have not provided evidence of secondary considerations that, when weighed with the evidence favoring obviousness, shows that claim 1 would have been nonobvious. Claims 5–14, 17–19, and 21 were not argued separately and fall with claim 1.

Rejection Nos. 2–7

Appellants do not contest Rejections 2–7. Accordingly, the rejections of claims 15, 16, 20, and 22–24 are affirmed. *See* 37 C.F.R. § 41.41(b)(2); *Hyatt v. Dudas*, 551 F.3d 1307, 1314 (Fed. Cir. 2008).

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SUMMARY

We affirm the rejections of all claims on appeal.

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