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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ERIN JEAN FINEHOUT, JOHN RICHARD NELSON, and PATRICK MCCOY SPOONER [1]

Appeal 2014-002891
Application 12/972,236
Technology Center 1600

Before ERIC B. GRIMES, ULRIKE W. JENKS, and TAWEN CHANG, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims directed to a method of extracting DNA from a biological sample. The Examiner rejects the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] According to Appellants, the real party in interest is General Electric Company. (App. Br. 1.)

STATEMENT OF THE CASE

Claims 1–25 are on appeal, and can be found in the Claims Appendix of the Appeal Brief. Claim 1 is representative of the claims on appeal, and reads as follows:

> 1. A method for extracting genetic material from a biological sample stored on a solid medium, comprising:
>
> obtaining the solid medium, wherein the biological sample is applied on the solid medium, and the solid medium comprises chemicals that lyse the biological sample and preserve the genetic material; and
>
> electroeluting the genetic material directly from the solid medium to a subsequent medium.

The other independent claims, claims 13 and 25, similarly recite electroeluting the genetic material directly from a solid medium.

Appellants request review of the following rejections:

I. claims 1–5 under 35 U.S.C. § 103(a) as unpatentable over Orlandi[2] in view of Mullis[3];

II. claims 6–9 under 35 U.S.C. § 103(a) as unpatentable over Orlandi in view of Mullis and further in view of Evans[4];

III. claims 10, 11, and 13–20 under 35 U.S.C. § 103(a) as unpatentable over Orlandi in view of Mullis and further in view of Shi[5];

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[2] Orlandi and Lampell, *Extraction-Free, Filter-Based Template Preparation for Rapid and Sensitive PCR Detection of Pathogenic Parasitic Protozoa*, 38 J. Clin. Micro. 2271–77 (2000) ("Orlandi").
[3] Mullis, US 5,187,083, issued Feb. 16, 1993 ("Mullis").
[4] Evans et al., US 2006/0088868 A1, published Apr. 27, 2006 ("Evans").
[5] Shi et al., *DNA Extraction from Archival Formalin-fixed, Paraffin-embedded Tissue Sections Based on the Antigen Retrieval Principle: Heating Under the Influence of pH*, 50 J. Histochem. & Cytochem. 1005–11 (2002) ("Shi").

IV. claim 12 under 35 U.S.C. § 103(a) as unpatentable over Orlandi in view of Mullis and further in view of Ahokas[6];

V. claims 21–23 under 35 U.S.C. § 103(a) as unpatentable over Orlandi in view of Mullis and further in view of Shi and Evans;

VI. claim 24 under 35 U.S.C. § 103(a) as unpatentable over Orlandi in view of Mullis and further in view of Shi and Ahokas; and

VII. claim 25 under 35 U.S.C. § 103(a) as unpatentable over Orlandi in view of Evans and Mullis.

I. and III.–VI. Obviousness over Orlandi and Mullis

The Examiner rejected claims 1–5 as obvious over Orlandi and Mullis, and rejected claims 10–24 over those references further combined with Evans, Shi, Ahokas, or combinations thereof. The issue presented is whether the combination of Orlandi and Mullis teaches the step of electroeluting genetic material from a solid medium. Because the same issue is dispositive for each of the rejections based on the combination of Orlandi and Mullis, we will consider them together.

The Examiner finds that Orlandi teaches "obtaining a solid medium wherein a biological sample is applied on the solid medium (i.e. FTA filter paper), and the solid medium comprises chemicals that lyse the biological sample and preserve the genetic material" that can be analyzed by PCR (Non-Final Act.[7] 4). The Examiner recognizes that Orlandi does not

[6] Ahokas, *Electroelution of nuclei acid in microfuge tubes*, 15 Nuc. Acid Res. 6759 (1987) ("Ahokas").
[7] Non Final Office Action mailed Sept. 20, 2012 ("Non-Final Act.").

electroelute the genetic material from the filter and looks to Mullis for teaching this limitation (*id.*). The Examiner concludes:

> [I]t would have been *prima facie* obvious to the PHOSITA at the time of the invention to modify the method reasonably suggested by Orlandi et al. wherein the method of preparing target DNA for PCR taught by Mullis is used in place of the method of preparing target DNA for PCR taught by Orlandi et al. Please note that substitution of one well known method/reagent/material with known properties for a second well known method/reagent/material with [well] known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

(Non-Final Act. 4–5).

Appellants contend: that there is no objective reason to combine the references (Reply Br. 4 ("adding additional steps to the method of Orlandi <u>increases the likelihood of losing some of the DNA</u>"; *see* App. Br. 6)); that the combination lacks reasonable expectation of success (Reply Br. 5 (references cited by the Examiner "merely disclose *amplification* and/or *sequencing* of genetic material fixed on a solid substrate")); *see* App. Br. 12 & 16); that the references teach away from the combination (App. Br. 6); and that the combination as proposed by the Examiner requires hindsight (App. Br. 9 ("it appears unlikely that the electroelution taught in Mullis would be a desirable modification to the method in Orlandi" because it requires cherry-picking the references for selected language)).

Does the preponderance of evidence of record support the Examiner's conclusion that electroelution of genetic material from a solid support is obvious based on the combination of Orlandi and Mullis?

Findings of Fact

FF1. Orlandi teaches that FTA™ disks[8] are "impregnated with denaturants, chelating agents, and free-radical traps . . . , caus[ing] most cell types to lyse on contact . . . and sequester[ing] DNA within the matrix. Cell remnants, sample debris, and other factors that may interfere with PCR are effectively removed by briefly washing the filters. " (Orlandi 2272).

FF2. Orlandi teaches that "crude biological samples could be applied directly to individual filters without prior purification steps or any substantial loss in detection signal. Formalin fixation did not appreciably affect sensitivity" (Orlandi 2273).

> Preparation of DNA templates from FTA filters was therefore rapid, uniform, and reproducible. DNA losses were avoided, as additional purification steps were not needed. Likewise, these filters preserved DNA integrity and eliminated potential sources of target DNA losses through degradative processes normally associated with conventional methods.

(Orlandi 2276).

FF3. Orlandi teaches that "washed filters were then used directly as the source of template in PCR" (Orlandi 2272, Material and Methods).

FF4. Mullis teaches obtaining DNA from biological samples. The method lyses cell membranes to yield "genomic DNA in a high molecular

[8] FTA (Life Technologies, Gaithersburg, Md) (Orlandi 2272, Materials and Methods).

weight form. The lysate is moved through a porous filter to selectively trap the high molecular weight DNA on the filter," and releasing the DNA from the filter (Mullis Abstract; *see* 3:30–42).

FF5. Mullis describes several techniques to release the trapped DNA from the filter. The techniques include cleaving the DNA chains, freeze thawing the filters, and dissolving the filters (*see id.* at 14:9–36). "Alternatively, the DNA trapped on the filter can be released by application of an electric field, such as in electroelution of DNA molecules from agarose gels" (*id.* at 14:23–26).

FF6. Mullis teaches "polymerase chain reaction amplification of DNA sequences trapped, recovered or otherwise purified by the present method. DNA trapped and purified on the filter of the present invention can lend itself to other analytical procedures" (*id.* at 14:30–34).

Principle of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 416 (2007).

Analysis

We have reviewed Appellants' contentions that the Examiner erred in rejecting the claims as obvious over the Orlandi and Mullis. (App. Br. 7–12.) We disagree with Appellants' contentions and adopt the findings concerning the scope and content of the prior art and reasoning set forth in

the Examiner's Answer, Final Office Action[9], Non-Final Action and Advisory Action[10]. We address Appellants' arguments below:

Appellants contend that there is no objective reason to combine the references (Reply Br. 4; App. Br. 6) and that the combination lacks a reasonable expectation of success (Reply Br. 6; App. Br. 12 & 16). Appellants assert that there is no "reason for electroeluting the limited amount of DNA on the FTA filter paper in Orlandi; especially, when it is desired to utilize that small amount of DNA on the FTA filter paper in the PCR reaction" (App. Br. 8). We are not persuaded by Appellants' contention.

As the Examiner explains "it was known at the time of the invention that so called 'dirty DNA preps' can lead to spurious PCR results (e.g. false negatives)" as evidenced by Orlandi (Ans. 3–4; FF1). Orlandi provides a simple method for capturing DNA that does not require a separate lysis and purification step (FF1 & FF2). Although Orlandi discloses that small DNA samples can be directly captured and assayed by PCR, the reference, however, does not otherwise limit the amount of DNA that can be captured by the FTA filter. As the Examiner recognizes, Orlandi does teach that the FTA DNA capture method allows for the removal of matrix-derived factors that are often present in prior art recognized isolation and purification procedures (*see* Orlandi 2271–72; Ans. 4). The removal of these matrix-derived factors by briefly washing the filters simplifies the purification procedure to obtain the desired genetic material (FF1). In addition to the two step purification procedures disclosed in Mullis (FF5 & FF6), the

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[9] Final Office Action mailed March 29, 2013 ("Final Act.").
[10] Advisory Action mailed June 14, 2013 ("Adv. Act.").

reference also requires a lysis step prior to applying the sample to the filter (FF4). We agree with the Examiner's position that incorporation of

> an additional purification step(s) (e.g. the electroelution step as taught by Mullis) into the method of Orlandi et al. in order to ensure that the template DNA was as clean as possible, prior to the PCR amplification step of Orlandi et al. and in order to prevent, as much as possible, any false or misleading results[,]

is within the grasp of the ordinary artisan (Ans. 4). "In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.,* 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations and citations omitted).

We recognize, but are not persuaded by, Appellants' contention that one of ordinary skill would not electroelute a limited DNA sample from a filter. Just because Orlandi suggests that the filters can be used directly for PCR does not mean that additional purification steps would not be desirable to further minimize the interfering factors (FF3, FF5, & FF6; *see* Ans. 4). There is also no disclosure in Orlandi that the FTA filter method is limited in the amount of DNA that can be captured. In other words, the reference is not limited to the use of only small DNA samples. Moreover, it is well settled that "in a section 103 inquiry, 'the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'" *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)).

Appellants contend that the references teach away from the combination (App. Br. 6). We recognize, but are not persuaded by, Appellants' contention that Orlandi would teach away from including any

additional purification steps, such as electroeluting the DNA sample before performing any additional assay procedures (*see* App. Br. 7–8). "A reference does not teach away . . . if it merely expresses a general preference for an alternative invention but does not 'criticize, discredit, or otherwise discourage' investigation into the invention claimed." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (citing *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004)). Although Orlandi is focused on obtaining results from the smallest sample size possible (*see* App. Br. 7), there is nothing in the reference that would indicate larger quantities of DNA cannot be applied to the FTA filter for the purpose of capturing and preserving the DNA sample for later analysis as disclosed in the reference (FF1–FF3).

Appellants contend that the combination as proposed by the Examiner requires hindsight (App. Br. 9). We are also not persuaded by this argument.

While we are fully aware that hindsight bias often plagues determinations of obviousness (*Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966)), we are also mindful that the Supreme Court has clearly stated that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416. Here, the combination of references teaches that before undergoing PCR analysis, it is important to purify the genetic material and remove any interfering factors before subjecting the material to further analysis steps (FF1–FF6). That the combination of references may suggest multiple ways of purifying the genetic material does not make any one purification process any less obvious over another.

We conclude that the evidence cited by the Examiner supports a prima facie case of obviousness with respect to claim 1, and Appellants have not provided sufficient rebuttal evidence or evidence of secondary considerations that outweighs the evidence supporting the prima facie case. As Appellants do not argue the claims separately, claims 2–5 and 10–24 fall with claim 1. 37 C.F.R. § 41.37 (c)(1)(iv).

II. & VII. Obviousness over Orlandi, Mullis, and Evans

The Examiner rejected claims 6–9 and 25 over the combination of Orlandi, Mullis, and Evans.

Appellants contend that the references are "silent with regard to repairing genetic material on a solid medium" (Reply Br. 5; App. Br. 11–12, and 16). We are not persuaded by Appellants' contention.

The combined teachings of Orlandi and Mullis is addressed above (*I. & III.–VI.*). The Examiner's position is that "the repair of a template DNA before its use as a template in a PCR assay was known" and therefore including such a step would have been obvious to one of ordinary skill in the art (Non-Final Act. 7). The Examiner relies on Evans for teaching a "universal enzyme mixture [that] can be used prior to or during polynucleotide amplification or other synthesis" in order to repair the DNA (Evans ¶ 100; Non-Final Act. 7). Evans teaches that genetic material may be repaired using "a reaction mixture that includes a ligase and a cofactor selected from NAD+ or ATP" and additionally includes an AP endonuclease and a polymerase (Evans, Abstract, ¶¶ 98 and 99). The Examiner explains that "the enzymatic manipulation of genetic material attached to a solid support(s) was well known and routine in the art at the time of the invention

(Official Notice)" citing Rovera[11], Peponnet[12], and Adessi[13] as support (Final Act. 5). Because it was known that genetic material can be acted on by enzymes while on a solid support there is no reason to doubt that the enzymes forming Evans' universal enzyme mixture would also be able to access and act on the genetic material on a solid support.

Although we agree with Appellants that Evans does not disclose the repair of genetic material on a solid surface itself, we do not agree with the premise that this would not be obvious based on the totality of the teachings in the prior art. Here, Orlandi already disclosed that a PCR reaction can be carried out while the genetic material is attached to a filter surface (FF1–FF3), a solid support. We agree with the Examiner's reasoning that once the ordinary artisan recognizes that the genetic material is available to be acted on by enzymes, for example those involved in a PCR reaction, there is no reason to doubt that enzymes involved in DNA repair, such as those disclosed in Evans' universal mixture, would also be able to access the captured genetic material. Evans explains that yields can be improved for polynucleotide amplification or other synthesis reaction. "This can be achieved, for example, when a damaged polynucleotide is treated with a preparation of enzyme(s) in a pre-incubation mixture and/or during amplification" (Evans ¶ 96, *see* ¶¶ 98–100). We find no error with the Examiner's conclusion that the combination of Orlandi, Mullis, and Evans would suggest incubating the genetic material prior to or during amplification with a universal enzyme mixture (*see* Non-Final Act. 7 and

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[11] Rovera et al., US 6,221,635 B1, issued Apr. 24, 2001 ("Rovera").
[12] Peponnet, US 6,277,604 B1, issued Aug. 21, 2001 ("Peponnet").
[13] Adessi et al., US 7,115,400 B1, issued Oct. 3, 2006 (Adessi").

18–19) that allows for the repair of the genetic material for improved amplification yields.

We conclude that the evidence cited by the Examiner supports a prima facie case of obviousness with respect to claims 6 and 25, and Appellants have not provided sufficient evidence of secondary considerations that outweighs the evidence supporting the prima facie case. As Appellants do not argue the claims separately, claims 7–9 fall with claim 6.

SUMMARY

We affirm the rejections of all claims.

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