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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte GARY MCMASTER, JOAN DAVIES, YUNQING MA, and YULING LUO,[1]

Appeal 2014-004283
Application 13/068,727
Technology Center 1600

Before DONALD E. ADAMS, MELANIE L. MCCOLLUM, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellants appeal under 35 U.S.C. § 134(a) from the final rejection of claims 20, 22–28, and 48. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

According to the Specification, the invention relates to "nucleic acid extraction and quantitation from cells and tissues," wherein "[n]ucleic acids are extracted from embedded clinical samples without the use of hydrophobic solvents." Spec. ¶ 2.

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[1] Appellants identify the real party-in-interest as Affymetrix, Incorporated. App. Br. 1.

> In a general aspect, a method of collecting a nucleic acid from cells associated with a hydrophobic component can include suspending the sample, incubating the sample and separating nucleic·acids from the sample and hydrophobic component. The sample of cells or tissue with the hydrophobic component melting at a temperature greater than 40°C can be suspended in an aqueous solution. The suspension can be incubated at a temperature higher than 40°C under conditions substantially non-denaturing to double stranded DNA of the cells, so that the hydrophobic component melts and the nucleic acid is released from the cells into the aqueous solution. Finally, the aqueous solution can be physically separated from the hydrophobic component, after the incubation, to collect the nucleic acid released from the cells.

Id. ¶ 14.

Claims on Appeal

As claimed, the invention relates to methods of determining a number of test cells as compared to a reference population based on the quantitation of ribosomal DNA (rDNA). The test cells may be tumor cells, cells on a microscope slide, or formalin-fixed paraffin embedded (FFPE) cells.

Claims 20, 22–28, and 48 are on appeal. Claim 20, the sole independent claim before us recites:

> 20. A method of determining a number of test cells, the method comprising:
>
> obtaining a reference nucleic acid sample from a known number of reference cells;
>
> quantitating an amount of a ribosomal DNA in the reference sample;
>
> providing a standard function for the reference cell number versus the reference ribosomal DNA quantity;

obtaining test cells selected from the group consisting of: tumor cells, cells on a microscope slide, and FFPE cells;

obtaining a test nucleic acid sample from the test cells;

quantitating an amount of the ribosomal DNA in the test sample; and,

determining a test cell number based on the standard function and the quantity of test ribosomal DNA.

Grounds of Rejection[2,3]

I. Claims 20, 22–28, and 48 stand rejected under 35 U.S.C. § 101 as drawn to non-statutory subject matter. Ans. 2.

II. Claims 20, 25–28, and 48 stand rejected under 35 U.S.C. § 102(b) as anticipated by Crocetti.[4]

III. Claims 20, 25–28, and 48 stand rejected under 35 U.S.C. § 103(a) as obvious over Crocetti.

IV. Claims 20, 22–28, and 48 stand rejected under 35 U.S.C. § 103(a) as obvious over Crocetti, Mann,[5] and statements in the instant Specification.

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[2] The Examiner has withdrawn previously entered rejections for lack of utility, failure to comply with the written description requirement, and for lack of enablement. Ans. 3.

[3] The Examiner raised new grounds of rejection under 35 U.S.C. §§ 102 and 103 in the Answer. *See id.* at 3. As Appellants address the substance of these rejections in the Reply, we consider them here. *See* Reply Br. 3, 7–10.

[4] Crocetti et al., US 2003/0170654 Al, published Sept. 11, 2003.

[5] Mann et al., US 6,365,364 B1, published Apr. 2, 2002.

I

We have reviewed Appellants' contentions that the Examiner erred in rejecting claims 20, 22–28, and 48 as drawn to non-statutory subject matter under 35 U.S.C. § 101. App. Br. 3–12; Reply 4–6. We disagree with Appellants' contentions and agree with the Examiner's findings and conclusion. *See* Ans. 2–15, 19–23. We provide the following comments for clarity and emphasis.

Section 101 of the Patent Statute broadly provides that, "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." Supreme Court precedents, however, provide three specific exceptions to the broad categories of § 101: laws of nature, natural phenomena, and abstract ideas. *Bilski v. Kappos*, 561 U.S. at 625. "The 'abstract ideas' category embodies the longstanding rule that '[a]n idea of itself is not patentable.'" *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (citing *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)).

In *Alice*, the Supreme Court referred to the two-step analysis set forth in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012), as providing "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." *Alice*, 134 S. Ct. at 2355 (citing *Mayo*, 132 S. Ct. at 1289). Under *Mayo*, "[w]e must first determine whether the claims at issue are directed to a patent-ineligible concept." *Id.* Next, "we consider the elements of each claim both individually and 'as an ordered combination' to determine whether the additional elements

'transform the nature of the claim' into a patent-eligible application." *Id.* (citing *Mayo*, 132 S. Ct. at 1297–98).

To be patentable under *Mayo*, a claim must do more than simply state the law of nature or abstract idea and add the words "'apply it.'" *Mayo*, 132 S. Ct. at 1294; *Benson*, 409 U.S. at 67. Likewise, "[s]imply appending conventional steps, specified at a high level of generality," is not "*enough*" for patent eligibility. *Alice*, 134 S. Ct. at 2357 (quoting *Mayo*, 132 S. Ct. at 1300).

With respect to step one of the *Mayo/Alice* analysis, we agree with the Examiner that the claims on appeal are drawn to a natural phenomenon or law of nature, in particular, that a "natural correlation exists between the amount of rDNA and the number of cells from which rDNA has been obtained." *See* Ans. 9–10.

In accord with step 2 of the *Mayo/Alice* framework, we are satisfied that the Examiner correctly considered the elements of each claim both individually and as an ordered combination to determine whether the additional elements transform the nature of the claim into a patent-eligible application. *See id.* at 10–11. Accordingly, we agree with the Examiner that the recited claim steps "amount to instructions that are well-understood, routine, conventional activity, previously engaged in by those in the field[, that] add nothing specific to the natural principle that would render it patent-eligible."[6] *Id.* at 10, 22–23; *see also* 132 S. Ct. 1289, 1298 ("[T]he claims inform a relevant audience about certain laws of nature; any additional steps

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[6] Our determination includes the mental steps of "normalizing a result" and "determining and efficiency" limitations of dependent claims 27 and 28, which Appellants briefly address. *See* App. Br. 9; Reply Br. 5–6; Ans. 8.

consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately.'). In sum, the claims before us merely inform the relevant audience of certain laws of nature: specifically, the relationship between the amount of rDNA and the number of cells from which rDNA has been obtained. *See Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1379–80 (Fed. Cir. 2016), *cert. denied*, (U.S. Oct. 3, 2016) (finding claims unpatentable under § 101 where, "the novelty of looking to non-coding DNA to detect a coding region allele of interest resides in the novelty of the newly discovered natural law of linkage disequilibrium between coding and non-coding regions and adds little more than a restatement of the natural law itself").

Appellants argue that the claimed "method[s] do[] not monopolize methods of counting cells or use of rDNA." App. Br. 3. Appellants similarly argue that the invention as claimed "do[es] not provide a monopoly over a correlation between nucleic acids or rDNA and a number of cells." *Id.* at 11. We do not find these arguments persuasive. "While preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility. . . . Where a patent's claims are deemed only to disclose patent ineligible subject matter under the *Mayo* framework, as they are in this case, preemption concerns are fully addressed and made moot." *Ariosa Diagnostics, Inc. v. Sequenom, Inc.,* 788 F.3d 1371, 1379 (Fed. Cir. 2015), *cert. denied,* No. 15-1182, 2016 WL 1117246 (U.S. June 27, 2016); *see also Vehicle Intelligence & Safety LLC v. Mercedes–Benz USA, LLC*, 635 F. App'x 914, 918 (Fed. Cir. 2015), *cert. denied,* No. 15-1201, 2016 WL 1171121 (U.S. May 31, 2016) ("And while

assessing the preemptive effect of a claim helps to inform the *Mayo/Alice* two-step analysis, the mere existence of a non-preempted use of an abstract idea does not prove that a claim is drawn to patent-eligible subject matter.").

Appellants further appear to argue that the claims satisfy the "machine-or-transformation" test and/or comprise more than mere mental steps because claim steps involving "obtaining" a nucleic acid sample and "quantitating" an amount of ribosomal DNA expressly or inherently involve physical transformation. *See* App. Br. 4–5; Reply Br. 4–5. We do not find Appellant's argument persuasive.

The Supreme Court in *Bilski* held that the "machine-or-transformation test" is not determinative of unpatentability under § 101. *Bilski v. Kappos*, 561 U.S. at 604. Moreover, the steps Appellants rely on are no more transformative than the claim steps of "administering a drug" or "determining the level of 6-thioguanine" at issue in *Mayo* (132 S. Ct. at 1295). Nor are the steps of the instant claims any more transformative than the claim steps "obtaining a non-cellular fraction of [a] blood sample," "amplifying a . . . nucleic acid" from that fraction, and "performing nucleic acid analysis on the amplified nucleic acid," in *Ariosa*. *See* 788 F.3d 1371 at 1373–1374. In each case, the courts determined that the claims as a whole were unpatentable and the recited steps merely provided general instructions to apply routine, conventional techniques, where the only new and useful subject matter is the underlying unpatentable natural phenomenon itself. *See id.* at 1377. As noted in *Mayo*, such "[p]urely conventional or obvious [pre]-solution activity is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law." 132 S. Ct. 1289 at 1298 (internal quotations and citations omitted).

For the above reasons, we sustain the rejection.

II–IV

The Examiner rejects claims 20, 25–28, and 48 as anticipated and/or obvious over Crocetti; and further rejects claims 20, 22–28, and 48 as obvious over Crocetti in combination with Mann and statements in the instant Specification regarding the scope and content of the prior art. Ans. 12–18. Appellants oppose. Reply Br. 7–10.

Findings of Fact

FF1. Crocetti teaches methods for the identifying and quantifying polyphosphate-accumulating organisms (PAOs) in wastewater by identifying 16S rDNA sequences unique to those organisms using oligonucleotide probes or primers. Crocetti, Abstract, ¶¶ 1, 10, 41. In one embodiment, these 16S rDNA sequences are used to quantitate PAOs in a sample by hybridization.

> [T]his is done by comparing the signal obtained from the probe-nucleic acid hybrid with a reference standard or a number of standards. That is, a standard is constructed comprising a known number of cells or a known amount of PAO DNA and the signal from the standard used to give a quantitative measure of the cells or DNA in the test sample.

Id. ¶ 56. In one embodiment, fluorescence in situ hybridization (FISH) using PAO-specific probes is preferred. *Id.* ¶¶ 36, 51,

FF2. Crocetti Example 1 describes the development and use of PAO-specific FISH probes to analyze the bacteria in wastewater reactor sludges. *See id.* ¶¶ 64–125. The Example includes microscopic analysis, in which bacteria were "collected, fixed and probed." *Id.* ¶ 82. "FISH probed samples were viewed on both a Zeiss LSM510 and on a Zeiss

Axiophot" microscope. *Id.* "Generally all three designed PAO-probes, PA0462, PA065 1 and PA0846 . . . were applied to any one individual sample spotted on the slide." *Id.* ¶ 85. "Counts of α, β (including β1 and β2), and γ-Proteobacteria, Actinobacteria, and *Cytophaga-Flavobacterium* were determined as proportions of all Bacteria (according to probe EUB338; Bond et al., 1999a-see below for details of probes)." *Id.* ¶ 82; *see* ¶ 85, Table 4. "The micrographs shown in FIGS 2D and 2E . . . . clearly show that the PAO probes are specific for polyphosphate accumulating organisms." *Id.* ¶¶ 114–115.

FF3. Mann is directed to methods of making and using angiogenesis inhibitors. Mann, Abstract. According to Mann, suitable assays for measuring the activity of such inhibitors "include those that are capable of . . . quantifying the proliferation of specific cells such as endothelial cells and tumor cells." *Id.* at 12:55–65.

FF4. The instant Specification states: "Each ribosomal gene is part of a 43 kb repeat unit that can be divided into two regions: a 13.3 kb transcribed region which contains the highly conserved genes for 18S, 5.85 and 28S rRNA subunits of the ribosome, and a 30 kb non-transcribed spacer (NTS) (Gonzalez, L. I., Wu, S., Li, W., Kuo, A. B. and Sylvester, E. J. (1992) Nucleic Acids Res., 20, 5846-5847.)." Spec. 21–22.

Analysis

The Examiner finds that Crocetti discloses "1) preparing and using one or more standards, which can be based on a known number of cells, 2) the normalization of such results by comparing, as well as 3) knowing how much rDNA was known standard/control cells, and then using this to

compare with test rDNA, (determination of efficiency of test nucleic acid extraction)." Ans. 14. With respect to claim step "obtaining test cells selected from the group consisting of: tumor cells, cells on a microscope slide, and FFPE cells," the Examiner points to paragraph 82 of Crocetti as "teach[ing] performing microscopy of the cells." The Examiner construes such cells "as being on a microscope slide . . . from which cells are used in the analysis of rDNA." *Id.* at 13–14. In the context of the § 101 discussion, the Examiner construes the steps of "'obtaining' sample and reference rDNA . . . as not requiring the actual isolation of any rDNA from any cell," and thus reading on in situ hybridization. *Id.* at 6–7 (referencing Spec. ¶ 126).

Appellants contend that the Examiner fails to demonstrate that Crocetti teaches or suggests the subsequent claim steps of "obtaining a test nucleic acid sample from the test cells" and "quantitating an amount of the ribosomal DNA in the test sample," because the mere presence of cells on a slide "does not actually or inherently disclose obtaining cells from a slide, or quantitating nucleic acid obtained from such cells." Reply 7; *see also id.* at 8 ("It is not even alleged that Crocetti obtains nucleic acids from cells on a slide, or that Crocetti quantitates rDNA from a test sample of cells from a microscope slide.").

We agree with Appellants. The Specification focuses on the analysis of nucleic acids extracted from embedded clinical samples. *See* Spec. ¶¶ 2, 14. The Examiner's citation to an isolated passage in the Specification suggesting that a particular DNA detection methodology is applicable to in situ hybridization studies does not convince us that the step of "obtaining a test nucleic acid sample from the test cells" is reasonably construed to encompass in situ techniques. Because the Examiner does not allege that

this element is satisfied by Mann or any admission of prior art in the Specification, we reverse.

SUMMARY

I. We *affirm* the rejection of claims 20, 22–28, and 48 as drawn to non-statutory subject matter under 35 U.S.C. § 101.

II. We *reverse* the rejection of claims 20, 25–28, and 48 under 35 U.S.C. § 102(b) as anticipated by Crocetti.

III. We *reverse* the rejection of claims 20, 25–28, and 48 under 35 U.S.C. § 103(a) as obvious over Crocetti.

IV. We *reverse* the rejection of claims 20, 22–28, and 48 under 35 U.S.C. § 103(a) as obvious over Crocetti, Mann, and statements in the Specification.

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