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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MARK W. ESHOO and JOHN PICURI[1]

Appeal 2018-000127
Application 13/233,913
Technology Center 1600

Before ERIC B. GRIMES, RICHARD M. LEBOVITZ, and TAWEN CHANG, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal involves claims to a method for labeling a nucleic acid with an ozone labile dye and a buffer comprising a thiourea. The Examiner rejected the claims under 35 U.S.C § 103 as obvious. Appellants appeal under 35 U.S.C. § 134(a) the Examiner's determination that the claims are unpatentable. We have jurisdiction under 35 U.S.C. § 6(b). The rejection is reversed.

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[1] According to Appellants, the real party in interest is Ibis Biosciences, Inc. Appeal Br. 3.

STATEMENT OF THE CASE

The claims stand finally rejected by the Examiner as follows:

Claim 15, 17, 18, 31–34, 36, 38–40, and 42 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of William Branham et al. (*Elimination of Laboratory Ozone Leads to a Dramatic Improvement in the Reproducibility of Microarray Gene Expression Measurements,* BMC Biotechnology, 7(8):1–8 (2007)) ("Branham"), Lofquist et al. (US 3,822,996, issued July 9, 1974) ("Lofquist"), and McConnell (US 5,180,500, issued Jan. 19, 1993). Ans. 2; Pre-Appeal Conference Decision (noting that the Examiner inadvertently omitted claims 18 and 40 from the rejection).

Claims 29 and 41 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Branham, Lofquist, McConnell, and Somdeb Mitra et al. (*High-Throughput Single-Nucleotide Structural Mapping by Capillary Automated Footprinting Analysis*, Nucleic Acids Research 36(11):1–10 (2008)) ("Mitra"). Ans. 5.

Claims 37 and 43 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Branham, Lofquist, McConnell, and LV Wei et al. (*Single Molecule Fluorescence Fluctuations of the Cyanine Dyes Linked Covalently to DNA,* Science in China Series B: Chemistry, 52(8):1148–53 (2009) ("Wei"). Ans. 7.

Independent claim 15 and dependent claim 17 are representative of the appealed claims and read as follows:

> 15. A method for labeling a nucleic acid comprising placing an ozone-labile fluorescent dye in a buffer comprising one or more thioureas, and then contacting said fluorescent dye in said buffer comprising said one or more thioureas with said nucleic acid.

> 17. The method of claim 15, wherein said fluorescent dye comprises Cy5.

REJECTIONS BASED ON BRANHAM, LOFQUIST, & McCONNELL

All the rejections are based on the combination of Branham, Lofquist, and McConnell. The Examiner found that Branham teaches that "it is critical to remove ozone when performing DNA microarrays comprising the ozone-labile fluorescent dye Cy5 dye and cDNA" to improve "reproducibility of the elected ozone-labile fluorescent dye Cy5 as well as its fluorescent intensity." Ans. 2–3. The Examiner acknowledged that Branham does not teach the addition of thiourea to labeling buffer as required by the claims, but found that Lofquist teaches "that it is advantageous to add thiourea to ozone-sensitive dyes that comprise a series of carbon-carbon double bonds" and that it was art-recognized "that ozone attacks the double bond chemical moiety (ozonolysis) and quenches the intensity of the dye by disrupting the conjugated framework." Ans. 3–4. The Examiner further cited McConnell as teaching that "thiourea behaves as a scavenger in the presence of ozone," in which "it is oxidized by ozone from thiourea to urea while ozone is reduced to molecular oxygen, thus destroying its capacity to react on the double-bonds of the fluorescent dye." Ans. 4. Based on these findings, the Examiner found one of ordinary skill in the art would have had reason to utilize thiourea in a labeling buffer as claimed when using an ozone-labile Cy5 dye as claimed. *Id.*

Appellants contend that the Examiner provided "no evidence of fact or law in support of its speculation that the Office's combination of Branham *(i.e.,* nucleic acid labeling) with Lofquist *(i.e.,* carpet fading) and McConnell *(i.e.,* scale removal from the interior surfaces of industrial

equipment) was within the level of ordinary skill in the art at the time the claimed invention was made." Appeal Br. 16. Appellants also argue that one of ordinary skill in the art would not have had reason to combine Branham's method of protecting Cy5 dye from ozone using a filter system of Lofquist which describes different dyes and substrates for the different purpose of improving "dyefastness" in carpets. *Id.* at 19. Appellants also argue that McConnell utilizes a pH of 12 which would hydrolyze DNA and thus one of ordinary skill in the art would not have turned to it to combine with Branham. *Id.* at 19–20.

The Examiner responded to Appellants' arguments by stating that both Lofquist and McConnell are reasonably pertinent to Branham and the subject matter of the claims because Lofquist addresses "the problem of combating ozone degradation on ozone-susceptible fluorescent dyes that comprise a series of carbon-carbon double bonds with the addition of thiourea to the fluorescent dye composition" and McConnell explains the mechanism. Ans. 20–21.

We reverse the rejection.

It is well-established that there are two criteria to be applied when determining whether a reference is analogous prior art: (1) whether the reference is from the "same field of endeavor" as the claimed invention, and (2) if the reference is not within the same field of endeavor, "whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved." *In re Clay*, 966 F.2d 656, 658–59 (Fed. Cir. 1992). In this case, the Examiner does not find that Lofquist and McConnell are in the same field of endeavor as the claimed subject matter, but finds that

they are reasonably pertinent to the problem addressed by the claims. We do not agree that the evidence supports this conclusion.

Branham teaches that "Environmental ozone can rapidly degrade cyanine 5 (Cy5), a fluorescent dye commonly used in microarray gene expression studies." Branham 1 (Abstract). Branham discloses that microarrays utilize "cyanine dye-labeled cDNAs or cRNAs to DNA probes covalently attached to microscope slides." *Id.* at 2. Branham teaches that "each dye must remain intact from the completion of the hybridization process through the duration of the scanning process." *Id.* Branham teaches that the ozone oxidation "occurs primarily after the hybridization washing procedures have been completed and the microarray becomes exposed to air containing environmental ozone." *Id.* Branham solved the problem of ozone oxidation by using a carbon filter in its laboratory handling system. *Id.* at 1 (Abstract). The problem identified by Branham is therefore preventing ozone oxidation of Cy5 dye-labeled nucleic acids hybridized to DNA on microscope slides.

Lofquist is directed to solving a different problem.

Lofquist describes the object of its invention as "to reduce or prevent the fading of dyed nylon fabrics, such as nylon carpets, caused by ozone." Lofquist 1:20–22.

Lofquist states that "Dyes have a multiplicity of double bonds, and perhaps for this reason are very sensitive to ozone." *Id.* at 1:37–38.

Lofquist discloses several different dyes which are used in carpets and fabrics, none of which are Cy5 as disclosed in Branham. *Id.* at 1:40–65; *see also* Ans. 3 (structure of Cy5).

Lofquist also teaches that "High humidity is necessary to cause noticeable ozone fading. Apparently moisture permits the dye to have sufficient mobility to diffuse to the surface of the yarn where the destruction of the dye occurs." *Id.* at 1:66–69.

Lofquist discloses that "[a] method and composition have been found for improving the fastness of dyes when exposed to ozone in polycarbonamide fibers. The method consists of exposing the fibers to ozone in the presence of a water-soluble thiourea coated on the fiber." *Id.* at 2:7–11. The method of Lofquist involves coating the fiber with the thiourea compound. *Id.* at 4:27–37 (claim 1).

Thus, the problem identified and solved by Lofquist is of reducing or preventing the fading of dyed nylon fabrics cause by ozone (Lofquist 1:19−21). One reason for the problem, as explained by Lofquist, is because in high humidity the dye diffuses "to the surface of the yarn where the destruction of the dye occurs." *Id.* at 1:66–69. Lofquist solved the problem by coating the fabric fibers with thiourea. *Id.* at 2:7−11; 4:27–37 (claim 1). Lofquist is not merely protecting a dye with double-bonds from oxidation, but is protecting specific dyes utilized to dye fabric from ozone destruction in high humidity in which noticeable ozone fading occurs. The Examiner did not establish that a solution to this different problem, using different dyes than those utilized by Branham, would have been considered by one of ordinary skill in the art to be reasonably pertinent to labeling nucleic acids as claimed and hybridizing such labeled nucleic acids to DNA arrays on microscope slides as described by Branham. The Examiner focused on the mechanism for ozone oxidation as described in McConnell, but knowing the

mechanism does not provide a solution to it or a reason to apply Lofquist's solution to a very different problem to Branham and the claims.

For the foregoing reason, the obviousness rejection of claim 15 is reversed. Independent claim 38, and dependent claims 17, 18, 29, 31–34, and 36–43, also require thiourea in a labeling buffer and the rejection of these claims is reversed for the same reason.

REVERSED