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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte NAOYUKI TOGAWA

Appeal 2019-004234
Application 13/984,373
Technology Center IP00

Before ERIC B. GRIMES, DEBORAH KATZ, and
ULRIKE W. JENKS, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge.*

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from Examiner's decision to reject claims 1, 3–6 and 9–18. We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

STATEMENT OF THE CASE

The Specification describes an "on-chip PCR reaction utilizing a gel-held type DNA microarray utilizing the molecular sieving effect of the spot gel." Spec. ¶ 1. High hybridization efficiency is achieved when using porous gels as opposed to already-known gel DNA microarrays. *Id.* ¶ 9. By

[1] We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a). Appellant identifies the real party in interest as Mitsubishi Chemical Corporation. Appeal Br. 2.

adjusting "the gel concentration (the porous structure of the gel) according to the size (base length) of a nucleic acid to be amplified (nucleic acid as a detection target), the molecular sieving effect of the gel can be improved and the detection method having a higher specificity can be provided." *Id.* ¶ 18. The Specification describes that a "'reaction on a microarray' means a 'reaction in the entire reaction system including a microarray and a reaction solution', and does not particularly mean a reaction only on the surface of and in the inside of a gel in an array utilizing the gel." *Id.* ¶ 22.

Claims 1, 3–6 and 9–18 are on appeal, and can be found in the Claims Appendix of the Appeal Brief. Claim 1, reproduced below, is illustrative of the claimed subject matter:

> Claim 1: A method for detecting a nucleic acid, the method comprising:
>
> contacting a plurality of gels, in which a probe is immobilized, with a reaction solution comprising a nucleic acid that serves as a template for nucleic acid amplification, a primer set for nucleic acid amplification, a nucleotide unit and a DNA extension enzyme;
>
> subjecting the gels and the reaction solution to a heat cycle for performing a nucleic acid amplification reaction;
>
> selecting nucleic acid fragments having a specific base length from among the amplified nucleic acid fragments; and
>
> detecting the selected nucleic acid fragments,
>
> wherein:
>
> the selecting of the nucleic acid fragments having the specific base length occurs by utilizing a molecular sieving effect of the gels;
>
> the specific base length of the selected nucleic acid fragments ranges from 50 bases to 3000 bases;
>
> the plurality of gels are contained on a common substrate;
>
> each gel of the plurality of gels is held in a well or through-hole of the common substrate;
>
> a gel concentration of the gels in which the probe is immobilized is 2.5 to 5% by mass;
>
> a ratio (V/S) of a volume of each gel of the plurality of gels (V

(μm^3)) to the surface

area of the gel in which the probe is immobilized that is in contact with the reaction solution (S (μm^2)) is 50 or more; and

the common substrate comprises:

(i) hollow fiber containing carbon black; and

(ii) a resin material containing carbon black.

Appeal Br. 18 (Claims Appendix)

REFERENCE(S)

The prior art relied upon by Examiner is:

Name	Reference	Date
Nagahama et al. ("Nagahama")	US 2006/0084060 Al	Apr. 20, 2006
Takahashi et al. ("Takahashi")	JP 2005249702 A	Sept. 15, 2005
Grunenwald, *Optimization of Polymerase Chain Reactions*, Methods in Molecular Biology Vol. 226: PCR Protocols, edt. J. M. S. Barilell and D. Stirling		
Strizhkov et al., *PCR Amplification on a Microarray of Gel Immobilized Oligonucleotides: Detection of Bacterial Toxin- and Drug-Resistant Genes and Their Mutations*, 29 Bio Techniques 844–57 (2000) ("Strizhkov")		
Yershov et al., DNA analysis and diagnostics on oligonucleotide microchips, 93 Proc. Natl. Acad. Sci. USA, 4913–18 (1996) ("Yershov")		

REJECTION(S)

Appellant requests review of the following grounds of rejection made by Examiner:

I. Claims 1, 3–6, 9, 10 and 15–18 under 35 U.S.C. § 103(a) as unpatentable over Strizhkov, as evidenced by Yershov, in view of Nagahama, and further in view of Takahashi.

II. Claims 1, 3–6 and 9–18 under 35 U.S.C. § 103(a) as unpatentable over Strizhkov, as evidenced by Yershov, in view of Nagahama and Takahashi, and further in view of Grunenwald.

Obviousness over Strizhkov, Yershov, Nagahama, and Takahashi

Because both of the rejections turn on the same issues, we will consider the rejections together. The issue with respect to these rejections is whether the preponderance of evidence of record supports Examiner's conclusion that the method of detecting nucleic acids held in a gel substrate that is formed as a well or through hole is obvious?

Findings of Fact

FF1. Strizhkov teaches "PCR amplification on a microarray of gel-immobilized compounds on a chip (MAGIChip™)." Strizhkov 844. "A microchip for PCR amplification contained about 1 pmol oligonucleotide primers immobilized through their 5' terminal amino groups inside 100 x 100 x 20-μm polyacrylamide gel pads or 100 x 100 x 40-μm porous mixed polyacrylamide gel pads spaced by a 200-μm hydrophobic glass surface." *Id.* at 845.

FF2. Strizhkov teaches using standard acrylamide gels (citing Yershov) or porous gels containing 1.5% acrylamide. *Id*. at 845. "Porous gels are more advantageous, providing the faster diffusion rate of large molecules and the higher level of amplification than the standard ones, but they are less stable." *Id.* at 850.

FF3. Yershov, cited by Strizhkov, teaches "[a] matrix of glass-immobilized gel elements was prepared as described [] by polymerization of 20-μm thin polyacrylamide (8% acrylamide/0.28% bisacrylamide) gel on a glass surface treated by Bind-Silane (LKB)." Yershov 4914.

FF4. Strizhkov teaches that "[s]tandard and porous [] gels have been used for PCR amplification and are accessible to globular proteins of about

100 kDa in size and to DNA of 100-150 bp and about 400 bp, respectively." Strizhkov 850.

FF5. Strizhkov teaches amplifying *B. anthracis* PCR products, specifically, "[t]he 103-bp *lef* fragment" and "the 248-bp *pag4* fragment." *Id.* at 845.

> Amplification of the anthrax toxin gene fragments. Microchip gel pads contained the immobilized forward *lef*-F [] or *pag4*-F primers. The PCR amplification solution contained the unbound forward *lef*-F and *pag4*-F primers, fluorescently labeled reverse *lef*-R and *pag4*-R primers and either *lef* or *pag4* products. The kinetics of amplification was monitored in real time as the accumulation of fluorescently labeled duplexes formed by the extended immobilized *lef*-F primer (curve 1) or *pag4*-F primer (curve 2) and the complementary DNA strands of either *lef* (A) or *pag4* (B) products.

Id. at 850 (legend Figure 2).

> The PCR buffer contained 2.5 mM $MgC1_2$, 10 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.1 % bovine serum albumin (BSA) (Sigma), 200 μM each dNTP (Sigma), 5 U AmpliTaq® DNA polymerase, Stoffel Fragment of *Taq* DNA polymerase (Applied Biosystems, Foster City, CA, USA), 1-10 pmol each of the forward unlabeled and reverse labeled primers and 10^4 copies of bacterial genomic or product DNA.

Id. at 845.

FF6. Nagahama teaches "a gel containing 2%-7% by mass of N,N-dimethylacrylamide and a biological substance immobilized on and/or in the gel." Nagahama, Abstract, *see* ¶ 28 (more preferably a gel made up of "N,N-dimethylacrylamide is 2.5% to 5.0% by mass"). "Biological substances immobilized on and/or in the gel in the

microarray serve as capture probes for nucleic acids or proteins which hybridize or bind to the biological substances." *Id.* ¶ 52.

FF7. Nagahama teaches a biological substance-immobilized gel microarray, made of gel-filled hollow tubes. *Id.* ¶¶ 12–17. The "microarray which is obtained by allowing a plurality of the above gel-filled hollow tubes (e.g., hollow fibers) to be tied in a bundle and cutting the tube bundle in a direction intersecting with the longitudinal direction of the tubes." *Id.* ¶ 19.

FF8. Nagahama teaches that "[t]he hollow tubes . . . may each be used as a base unit for supporting the biological substance immobilized gel." *Id.* ¶ 46. Nagahama teaches that the spaces between the hollow fibers are filled with resin (*id.* ¶ 48) and that the resin material is supplemented with carbon black. *Id.* ¶ 59.

FF9. Nagahama teaches hollow tubes wherein the "surface area of each compartment is preferably 10^{-6} m^2 or less." *Id.* ¶ 18. "[H]ollow fibers with an outer diameter of 0.3 mm, an inner diameter of 0.2 mm." *Id.* ¶ 57. Additionally, the hollow fibers have a thickness of about 500 μm (0.5 mm). *Id.* ¶ 70.

FF10. Takahashi[2] teaches a DNA chip made up of hollow tubular bodies. Takahashi, Abstract. Takashi teaches filling the hollow tubes with the gel-like substance made of acrylamide containing 2 to 20% acrylamide monomer by mass. *Id.* at 11. Takahashi teaches incorporating materials that can detect biological substances, such as nucleic acid, into the gel. *Id.*

[2] Takahashi is not paginated, we refer to page numbers of Takahashi as if it was numbered consecutively beginning with the first page.

FF11. Takahashi teaches a hollow tubular body having a diameter of 0.32 mm and a thickness of 0.1 mm. *Id.* at 12.

FF12. Takahashi teaches that in order to reduce noise "the hollow tubular body containing an appropriate amount of black pigments, such as carbon black." *Id.* at 12. The hollow tubular bodies of Takahashi are made of polycarbonate and contain 1% carbon black. *Id.* at 12.

Principle of Law

"If the claim extends to what is obvious, it is invalid under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007). "The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425 (CCPA 1981). "[O]ne cannot show non-obviousness by attacking references individually where, as here, the rejections are based on combinations of references." *Id.* at 426.

Analysis

Examiner finds that Strizhkov teaches most of the elements recited in the claims such as immobilizing oligonucleotides in a porous gel, subjecting the gels to a reaction solution, and applying heat cycles for performing a nucleic acid amplification reaction. Non-Final Act.[3] 3; FF1–FF5. Examiner acknowledges that Strizhkov does not exemplify the recited gel concentration, or that the gel is held in a well or through hole on a common

[3] Non-Final Office Action mailed March 27, 2018 ("Non-Final Act.").

substrate containing hollow fibers and resin that include carbon black. Non-Final Act. 4. Examiner relies on the teachings of Nagahama and of Takahashi for disclosing these limitations. Non-Final Act. 4; FF6–FF12.

Examiner concludes that

> [o]ne [of ordinary skill in the art] would have been motivated to employ an array of gel-filled hollow fibers instead of gel pads because this facilitates the mass production of large numbers of identical microarrays upon bundling of the gel-filled fibers with an adhesive resin (e.g. [Nagahama] paragraphs [0013]-[0017] and [0046]-[0051]), which is ideal for performing PCR analysis on multiple different samples.

Non-Final Act. 5. Examiner concludes that based on the teachings Nagahama, one would of been motivated to employ gels having an acrylamide concentration between 2.5 to 5% because "this gel composition is optimal for obtaining a uniform distribution of fluorescence intensity in each compartment and higher hybridization efficiency (e.g. [Nagahama] paragraphs [0007]-[0008], [0028], Working Example 1 and Figure 1, and Working Example 2 and Figure 2)." Non-Final Act. 5. Furthermore, Examiner concludes that based on the teachings of Takahashi "[o]ne [of ordinary skill in the art] would have been motivated to include carbon black in the hollow fibers and resin because so doing reduces background signal (or noise) during fluorescence measurement of nucleic acid signal." *Id.* at 6.

Appellant contends that there is no motivation to replace the gel pad of Strizhkov with cylindrical wells or through-holes because this would limit the diffusion of the DNA fragments into the gel, and thereby defeat a central objective of Strizhkov's process. *See* Appeal Br. 9, 14, 16; Reply Br. 3.

Claim 1

We have reviewed Appellant's contentions in light of the art cited by Examiner and find that Examiner has the better position. Examiner identifies the suitability for "mass production of large numbers of identical microarrays upon bundling of the gel-filled fibers with an adhesive resin" as taught by Nagahama as motivation to change Strizhkov's gel format. Ans. 4 (citing Nagahama ¶¶ 13–17, 46–51). Examiner identifies that Strizhkov already recognizes that their porous gel format is not ideal because the gel is prone to tearing. *Id.* at 5 (citing Strizhkov 850). Examiner finds that "the hollow tubes or fibers disclosed by Nagahama et al. serve as a base unit for supporting the advantageous gels of porous polyacrylamide." *Id.* at 5 (citing Nagahama ¶ 46 ("The hollow tubes . . . may each be used as a base unit for supporting the biological substance immobilized gel"). Examiner finds that

> Nagahama et al. explicitly recognize that there is a need in the field of capture oligonucleotide-immobilized gel microarrays for an improvement in the technology that addresses the issue faced by Strizhkov et al.: "there has been a problem that when the microarrays after hybridization are measured for fluorescence intensity in each of their compartments where capture probes are immobilized, the fluorescence intensity is higher in the outer regions of the compartments, but lower in the center regions of the compartments" (e.g. paragraph [0006]). Nagahama et al. describe their invention as meeting this need by providing a uniform distribution of fluorescence intensity in each compartment and a higher value for total fluorescence intensity summed over the entire area of each compartment (e.g. paragraph [0007]).

Id. at 5. Takahashi suggests adding carbon black to the hollow fiber tubes as another way to reduce noise from the gel imbedded hollow tubular bodies. FF12. Here, Examiner identifies mass-production of the microarray,

stabilizing the gel, in conjunction with improved fluorescent detection as motivation to modify Strizhkov's gel pads into gel filled hollow fiber tubes. We find no error with Examiner's identified motivation as a reasonable basis for concluding the claims are rendered obvious based on the combination of Strizhkov, Yershov, Nagahama, and Takahashi.

In support of their "no motivation" argument, Appellant contends that Examiner's proposed modification of Strizhkov would change its principle of operation and would render Strizhkov unsatisfactory for its intended purpose. Appeal Br. 9. Appellant relies on *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984) as legal authority for this contention. *Id.* While the proposed modification would result in a device with reduced surface area available for diffusion of substances into the gel matrix, the modified device still would operate according to the same principles as the unmodified device. Namely the imbedded oligonucleotide linked to the gel matrix would still capture complementary nucleic acid, therefore, the operation (i.e. function) of the bound oligonucleotide is still the same as in Strizhkov. Appellant's arguments with respect to the exposed surface area available for diffusing substances in and out of the gel matrix of the hollow tube is directed to the efficiency of the material flowing in and out of the gel, and is not directed to the change in function of the substances attached to the gel. Here, the combination as suggested by Examiner may result in decreased diffusion of materials in and out of the gel matrix but comes with the improved benefit of ease of production of the microarray as well as improved detection as taught in Nagahama, and Takahashi. *See* FF6–FF12; *In re Urbanski,* 809 F.3d 1237, 1243 (Fed. Cir. 2016) (holding that a combination of references may

be obvious even if the combination is at the expense of a benefit of one of the references).

We conclude, considering the totality of the cited evidence and arguments, that the preponderance of the evidence supports Examiner's conclusion of obviousness with respect to claim 1. Appellant has not provided sufficient rebuttal evidence or evidence of secondary considerations that outweighs the evidence supporting Examiner's conclusion. As Appellant does not argue the claims separately, claims 5, 6, 10, 9–14, 16–18 fall with claim 1. 37 C.F.R. § 41.37 (c)(1)(iv).

Claims 3 and 15

With respect to the rejections of claims 3 and 15, Appellant relies on the same arguments relied upon with respect to claim 1, discussed above. *See* Appeal Br. 13–16. Thus, for the reasons discussed above, we find that Examiner has established a prima facie showing of obviousness with respect to claims 3 and 15, which Appellant has failed to rebut. Accordingly, we affirm the rejection of these claims as well.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 3–6, 9, 10, 15–18	103	Strizhkov, Yershov, Nagahama, Takahashi	1, 3–6, 9, 10, 15–18	
1, 3–6, 9–18	103	Strizhkov, Yershov, Nagahama, Takahashi	1, 3–6, 9−18	
Overall Outcome			1, 3−6, 9−18	

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). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED