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SZDC Law P.C.
1629 K Street N.W.
Suite 300
Washington, DC 20006

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OYEYEMI, OLAYINKA A	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte YONG LIAO

Appeal 2019-004961
Application 15/559,054
Technology Center 1600

Before JEFFREY N. FREDMAN, DEBORAH KATZ, and JOHN G. NEW, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellant[1] seeks our review, under 35 U.S.C. § 134(a), of the Examiner's decision to reject claims 1–3 (Appeal Brief filed November 30, 2018 ("Br.") 5.)

We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as the inventor, Dr. Yong Liao. (*See* Br. 3.)

INTRODUCTION

Appellant's Specification provides a kit for quantitatively detecting hepatitis B virus covalently closed circular DNA ("cccDNA"). (Specification filed September 17, 2017 ("Spec.") ¶ 1.) The Specification discloses that cccDNA plays an important role in the replication of hepatitis B virus and the establishment of infection status. (*Id.* ¶ 4.) Hepatitis cccDNA is formed from incomplete closure Ring DNA ("rcDNA"). (*Id.* ¶ 3.) Hepatitis B virus rcDNA is characterized by a DNA fissure or gap region between two ends of the rcDNA. (*Id.*) The DNA fissure region is extended and repaired in the infected cell nucleus, thereby forming complete double-stranded cccDNA. (*Id.*) Methods for quantitative detection of cccDNA distinguish between cccDNA and rcDNA by identifying the presence or absence of a complete ring. (*Id.* ¶ 5.)

The Specification describes a prior art process for real-time quantitative PCR detection of cccDNA. (*Id.* ¶ 15.) The process uses a TaqMan probe with a light-emitting group and a quenching group. (*Id.*) If the negative strand is complete (cccDNA), a primer guides the Taq enzyme, which reaches and cleaves the bound TaqMan probe. (*Id.*) The light-emitting group is then released from the quenching group and produces a fluorescent signal. (*Id.*) However, if the negative chain is not complete (rcDNA), the upstream primer cannot pass through the chain gap, and the probe is not activated. (*Id.*) The Specification argues "this method is a gold standard for cccDNA quantification in clinical liver puncture specimens, but the specificity of this method is particularly low." (*Id.*) In contrast, the Specification asserts the invention is an improvement over the prior art by

using DNase that is safe for closed loop DNA to remove non-cccDNA; using a rapid, simple and inexpensive PCR to qualitatively detect cccDNA; and using a probe method and EvaGreen fluorescent dye method to conduct a digital PCR for absolute quantitative detection of cccDNA. (*Id.* ¶ 17.)

Appellant's claim 1 recites:

> A composition for detecting hepatitis B virus cccDNA, comprising
>
> an upstream primer consisting of the DNA sequence set forth in SEQ ID NO. 1,
>
> a downstream primer consisting of the DNA sequence set forth in SEQ ID NO. 2, and
>
> a probe consisting of the DNA sequence set forth in SEQ ID NO. 3 and a light-emitting group and a quenching group.

(Br. 12.) Independent claim 2 recites a kit including the primers and probe of claim 1, an extraction agent, ATP-Dependent DNase, a fluorescent dye, a first PCR DNA polymerase, and a second digital PCR DNA polymerase. (*Id.*)

The Examiner rejected the claims as follows:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Final Act.
1	103	Zhong,[2] GenBank,[3] An,[4] SantaLucia[5]	8–11
2, 3	103	Zhong, GenBank, An, SantaLucia, Xu[6]	11–13

ANALYSIS

The Examiner finds Zhong teaches a composition for detecting hepatitis B virus cccDNA using real-time PCR. (Final Office Action mailed June 29, 2018 ("Final Act. 9"), citing Zhong 1906.) The composition includes an upstream primer, a downstream primer, and a TaqMan probe including a light-emitting group, e.g., 6-carboxyfluorescein ("FAM"), and a fluorescent quencher, e.g., carboxytetramethylrhodamine ("TAMRA"). (*Id.*) The Examiner finds Zhong teaches that the cccDNA-selective primers and probe target the gap region between the viral genome's direct repeat regions, DR1 and DR2. (*Id.*) Specifically, the Examiner finds the primers consist of sequences disclosed by GenBank Accession No. KJ843187 as follows: the

[2] Zhong et al., *Quantitation of HBV covalently dosed circular DNA in micro formalin fixed paraffin-embedded liver tissue using rolling circle amplification in combination with real-time PCR*, 412 Clinica Chimica Acta 1905–1911 (2011).
[3] M. M. Gonzalez Lopez Ledesma et al., *Hepatitis B virus isolate Ag26, complete genome*, GenBank Accession No. KJ843187.1 (2014).
[4] An et al., US 2003/0050470 A1, published March 13, 2003.
[5] John SantaLucia, Jr., *Physical Principles and Visual-OMP Software for Optimal PCR Design*, *in* Methods in Molecular Biology 3–33 (Anton Yuryev ed. 2007).
[6] Xu et al., CN 101397592 A, published April 1, 2009. Machine translation made of record.

upstream cccDNA primer consists of nucleotides 1521–1538; the downstream cccDNA primer consists of nucleotides 1884–1868; and the cccDNA probe consists of nucleotides 1825–1845. (*Id.*)

The Examiner acknowledges that Zhong does not teach primers and a probe with the claimed sequences. (*Id.*) However, the Examiner finds that the claimed sequences were known in the prior art. (*Id.*) Particularly, GenBank Accession No. KJ8437187 teaches the complete genome of hepatitis B virus isolate Ag26, including sequences 100% identical to: SEQ ID NO.1 at nucleotides 1559–1576, SEQ ID NO.2 at nucleotides 1881–1864, and SEQ ID NO. 3 at nucleotides 1778–1800. (*Id.*, citing GenBank.)

The Examiner finds that An teaches an algorithm for designing various probes and primers based on disclosed nucleotides sequences. (*Id.* at 10, citing An ¶¶ 65–67.) The Examiner finds that "one of ordinary skill in the art would have recognized that the principles of designing primers and probes based on a disclosed nucleotide sequence would have applied to any nucleotide sequence under study." (*Id.*) The Examiner further finds that SantaLucia teaches that an experienced molecular biologist would have a reasonable expectation of success in "casually" designing primers and probes for a PCR reaction. (*Id.* at 10–11, citing SantaLucia 14.) The Examiner concludes it would have been obvious to a person of ordinary skill in the art to use alternatives known sequences in Zhong's detection composition for cccDNA, as it was matter of routine practice to select primer and probe sequences from known template sequences for amplifying and detecting HBV cccDNA. (*Id.*)

Appellant contends that GenBank does not teach or suggest any partial sequence that can be used as a primer or probe. (Br. 6.) Appellant argues that the skilled artisan would "need to conduct undue experiments to find suitable primers and probes" for detecting hepatitis B virus cccDNA. (*Id.* at 6–7.) Appellant argues that An and SantaLucia do not provide any guidance on the design of primers and probes for detecting hepatitis B virus. (*Id.* at 7.) Appellant argues therefore, that the combined prior art does not teach or suggest all of the elements of independent claims 1 and 2. (*Id.*)

We are not persuaded by Appellant's argument with respect to the scope of the prior art and the reasonable expectation of success. The Examiner cites Zhong for teaching that hepatitis B virus cccDNA primers and probes are designed by targeting the gap region between the two direct repeat regions (DR1 and DR2) of the viral genome. (Zhong 1906.) Zhong further teaches that the specificity and sensitivity of PCR quantitative detection methods depend on "preferential amplification of cccDNA by selective primers [] located on both sides of the gap of HBV relaxed circular DNA (rcDNA)." (*Id.* at 1905.) Contrary to Appellant's argument, the prior art provides specific guidance on designing primers and probes for detecting hepatitis B virus cccDNA. Following Zhong's teachings, it would have been obvious for a person skilled in the art to identify primers and probes in the region of base pairs 1500–1870 as overlapping the gap and direct repeat regions. "Obviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). Because the

prior art establishes a reasonable expectation of success, we are not persuaded that the Examiner erred.

Appellant also argues that "the claimed invention achieves superior and unexpected results." (Br. 8.) Specifically, Appellant asserts that Figure 5 of the Specification shows a detection level of 10^0 copies/μl and that "the lower limit of detection of cccDNA could reach a single copy." (*Id.*) Appellant contends that "the dynamic detection range of cccDNA in *Zhong* is 10^2 copies/ml to 10^{10} copies/ml." (*Id.*, citing Zhong 1908.) Appellant asserts that the "sensitivity of the present invention is 10–100 times better" than that of the prior art. (*Id.*)

The Examiner responds that Appellant's Specification discloses "a dynamic range of detection of HBV cccDNA at 10^5 copies/μL to 10^1 copies/μL using the instant primers and probe." (Examiner's Answer mailed April 2, 2019 ("Ans.") 12, citing Spec. ¶¶ 35, 90.) The Examiner finds that this dynamic range, converted to copies/ml overlaps Zhong's dynamic range. (*Id.*) Likewise, the Examiner finds that converting the units of Figure 5 from copies/μl to copies/ml results in a detection limit of 10^3 copies/ml, which falls within Zhong's dynamic range. (*Id.* at 13, citing Spec. ¶ 94.) Indeed, the evidence shows that Zhong teaches a "credible lower limit of the detection of HBV cccDNA was 0.01 copies/cell" (Zhong 1908).

We agree with the Examiner that Appellant's evidence is not probative of nonobviousness. "Unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (internal citations omitted). "Results which

differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time." (*Id.*) Appellant has not established that the allegedly superior and unexpected results are different in kind. Therefore, we are not persuaded of Examiner error.

Accordingly, we affirm the Examiner's rejection of claim 1. Appellant does not provide separate arguments for the rejection of the dependent claims. (*See* Br. 7, 10.) Accordingly, we affirm the Examiner's rejection of claims 2 and 3 as being obvious under 35 U.S.C. § 103.

CONCLUSION

Upon consideration of the record and the reasons given, the rejection of claims 1–3 is sustained.

In summary:

Claims Rejected	35 U.S.C. §	Basis	Affirmed	Reversed
1	103	Zhong, GenBank, An, SantaLucia	1	
2, 3	103	Zhong, GenBank, An, SantaLucia, Xu	2, 3	
Overall Outcome			1–3	

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED