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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HENRIK JOHANSSON and OLOF ERICSSON[1]

Appeal 2014-002943
Application 12/664,177
Technology Center 1600

Before DEMETRA J. MILLS, ULRIKE W. JENKS, and JOHN G. NEW
Administrative Patent Judges.

JENKS, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims directed to a method of introducing target nucleic acid molecules into a DNA sequence. 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 Agilent Technologies, Inc. (App. Br. 3.)

STATEMENT OF THE CASE

According to the Specification, the invention is directed to the field of multiplex DNA analysis. (Spec. 1.) The invention provides

> means to equip a target nucleic acid molecule population with both common sequence elements and individual sequence elements unique for single targets and or subpopulations within the selected target sequences. The common elements can subsequently be utilized for e.g. amplification of all selected target sequences while the individual sequence elements can be used for e.g. analysis, quantification or sorting of the respective target molecules.

(*Id.* at 3.)

Claims 1–7 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 (emphasis added):

> 1. A method for introducing common and/or individual sequence elements in a target nucleic acid molecule in a sample containing sample nucleic acid molecules, comprising the steps:
>
> i) *hybridizing a sample comprising single stranded nucleic acid molecules* with primary, secondary, and tertiary probe nucleic acid molecules, wherein the 3'-end of the tertiary probe comprises a part complementary to the primary probe and the 5'-end of the tertiary probe comprises a part complementary to a 5'-part of the target nucleic acid molecule; the 3'-end of the secondary probe is complementary to a 3'-part of the target nucleic acid molecule and the 5'-end of the secondary probe is not complementary to the target nucleic acid molecule; wherein said primary, secondary and tertiary probes comprise said common and/or individual sequence elements;
>
> ii) ligating the 3'-end of the primary probe to the 5'-end of the target nucleic acid molecule; and
>
> iii) introducing said common and/or individual sequence elements in said target nucleic acid molecule by elongating the

3'-end of the secondary probe or elongating the 3' end of the nucleic acid molecule, using a nucleic acid polymerase.

(App. Br. 10, Claims Appendix.)

Appellants seek review of the Examiner's rejection of claims 1–7 under 35 U.S.C. § 103(a) as unpatentable over Weismann.[2] Because the claims are not separately argued, we focus our discussion on representative claim 1. Claims 2–7 stand or fall with that claim. 37 C.F.R. § 41.37 (c)(1)(iv).

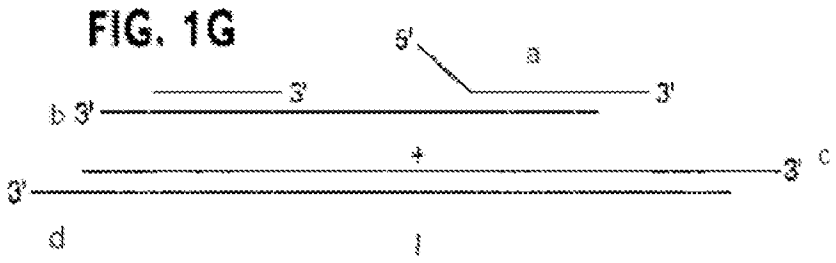
Obviousness over Weissman

The issue is: Does the preponderance of evidence of record support the Examiner's conclusion that Weissman teaches using single stranded nucleic acids in the hybridization steps as required by the method claimed?

Findings of Fact

We adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art as set forth in the Examiner's Answer and the Final Action dated April 4, 2013 ("Final Act."). For emphasis only we highlight the following:

FF1. The Examiner finds that Weissman's Fig 1G (reproduced below FF2) shows nucleic acids having "single stranded portions" (Ans. 8). The Examiner's annotated Fig. 1G is shown below:



[2] Weissman et al., US 6,576,448 B2, issued June 10, 2003.

Fig. 1G (Ans. 7) shows the Examiner's identified single stranded nucleic acid regions as a, b, c, and d (Ans. 8).

FF2. With reference to Fig. 1G-1I, reproduced below, Weissman discloses probes and primers for the production of a rolling circle amplification (RCA) template.

FIG. 1G

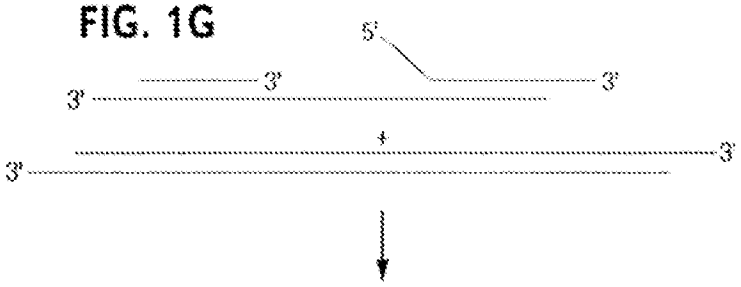


FIG. 1H

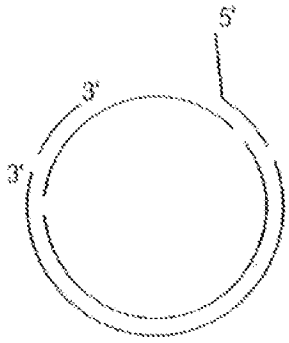


FIG. 1I

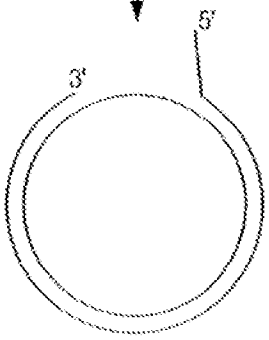


Fig. 1H-1I show, the hybridization of primers and subsequent circularization of the replication template.

A partially double-stranded adapter is used to circularize a double stranded DNA fragment for use as an RCA template. The adapter which has appropriate overhangs on its ends to

> allow ligation to both ends of the DNA fragment (FIG. lG) can be used such that annealing of the ends results in a circularized adapter-fragment construct (FIG. 1H) and ligation seals the nicks (FIG. 1I)
>
> (Weissman 5: 51–58).

FF3. Weissman also teaches that "[t]he single-stranded DNA product of rolling circle amplification can itself be replicated by annealing of complementary primers which can be extended in conventional primer elongation reactions or in hyberbranching reactions in which exponential amplification occurs" (Weissmann 3: 49–54).

FF4. The Specification provides that "depending on the source of nucleic acids, the sample may have to be prepared to some extent. If genomic DNA is used as source DNA it will advantageously be fragmented to achieve complete denaturation of the double stranded DNA *into single stranded DNA available to probe hybridization*" (Spec. 10 (emphasis added)).

FF5. The Specification provides that the method step includes "*denaturing* the sample nucleic acid molecules, if the sample nucleic acid molecules are double-stranded, *to obtain single stranded sample nucleic acid molecules*" (Spec. 3 (emphasis added)).

Analysis

We have reviewed Appellants' contentions that the Examiner erred in rejecting claims 1–7 as obvious over the cited art. (App. Br. 4–9.) We disagree with Appellants' contentions and adopt the findings concerning the scope and content of the prior art and conclusions set forth in the Examiner's Answer and the Final Act. For emphasis, we highlight and address the following:

Appellants contend that "Weisman's own disclosure makes it quite clear that his sample is denatured and then renatured to produce double strand molecules prior to hybridization with the oligonucleotides" (Reply Br. 3–4). Thus, "Weismann's suggestion to use molecules that are 'denatured and re-annealed' is not a suggestion to use single stranded nucleic acid molecules" as suggested by the Examiner (App. Br. 7). "[D]ouble stranded nucleic acid molecules are required in Weissman's method because only double stranded nucleic acid molecules . . . [are] capable of being amplified by rolling circle amplification" (*id.* at 6).

We are not persuaded. "[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000). The Examiner interprets that "[t]he claims require 'single stranded nucleic acids' however the claims do not specifically require the single stranded nucleic acids are completely single stranded or merely a portion is single stranded" (Ans. 8; *see also* Advisory Action[3] ("the claim can be broadly interpreted as having nucleic acid molecules which are partially or completely single stranded")). This interpretation is consistent with the Specification. The Specification clarifies that the need to be single stranded is to achieve hybridization with a probe (FF4 and FF5). Thus, the Specification makes it clear that the purpose of being "single stranded" is to achieve hybridization with the probes and primers. In light of the teaching of the Specification we find no error with the Examiner's claim interpretation that the nucleic acid sequence needs to be single stranded only so far and for so long that it

[3] Office Action dated June 14, 2013.

allows hybridization with the requisite probes and the nucleic acid that is the target for amplification.

The Examiner finds, and Appellants do not contest (*see* Reply Br. 3), that "denaturing of nucleic acids followed by re-annealing (or hybridization) to form heterohybrids inherently requires double stranded nucleic acids to denature forming single stranded nucleic acids so as to allow them to hybridize to another strand to form a heterohybrid" (Ans. 10; *see also* Advisory Action ("the claims as presented inherently require conditions that allow for the target nucleic acid and probe to be single stranded prior to the hybridization and annealing, which would include 're-annealing,' to provide conditions in which the complex of step i) is formed to allow for subsequent hybridization step"); *see* FF1 and FF2). Additionally, although not relied on by the Examiner in making the rejection, we note that Weissman teaches that the product of the rolling circle amplification is a single-stranded DNA that can be further processed using complementary primers in conventional reactions (FF3).

Appellants also contend that the Examiner's reliance on the language of claim 7 is in error because the claim "does not imply or suggest that the sample recited in claim 1 can be denatured and then reannealed to make double strands prior to starting the method of claim 1" (App. Br. 9).

We are not persuaded, as explained by the Examiner, the claimed method is not limited solely to the use of single stranded DNA, in other words, DNA that is single stranded for the entire length of the nucleic acid string. If double stranded DNA is used, then the additional step of preparing the sample to obtain single stranded DNA for the purpose of hybridizing probes to the DNA is needed as explained by the Specification (*see* FF4 and

FF5). The Examiner's point is that the claim language of claim 1 is open and can include additional steps (*see* Ans. 8), such as a denaturing step. *See Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."). We agree with the Examiner's interpretation that the inclusion of an additional step is encompassed by the method as set out in claim 1.

Based on the preponderance of the evidence of record, 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. Arguments not made are waived. *See* 37 C.F.R. § 41.37(c) (1) (iv).

SUMMARY

We affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as unpatentable over Weismann. Claims 2–7 were not separately argued and fall with claim 1. 37 C.F.R. § 41.37 (c)(1)(iv).

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