



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.
13/830,408 03/14/2013 BRIAN JON PETER 20110027-02 2259

22878 7590 11/20/2018
Agilent Technologies, Inc.
Global IP Operations
5301 Stevens Creek Blvd
Santa Clara, CA 95051

EXAMINER

LU, FRANK WEI MIN

ART UNIT PAPER NUMBER

1634

NOTIFICATION DATE DELIVERY MODE

11/20/2018

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPOPS.LEGAL@agilent.com
Agilentdocketing@cpaglobal.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte BRIAN JON PETER, ROBERT A. ACH,
ZOLTAN TIMAR, JOEL MYERSON,
JEFFREY ROBERT SAMPSON, and HOLLY HOGREFE¹

Appeal 2017-010159
Application 13/830,408
Technology Center 1600

Before RICHARD M. LEBOVITZ, JEFFREY N. FREDMAN, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal involves claims directed to methods of producing a double-stranded DNA product that comprises a triplex region. The Examiner rejected the claims as obvious under 35 U.S.C. § 103 and indefinite under 35 U.S.C. § 112. Pursuant to 35 U.S.C. § 134, Appellants appeal the rejection of the claims as unpatentable. We have jurisdiction under 35 U.S.C. § 6(b). The rejections are reversed.

¹ The Appeal Brief (“App. Br.”) lists Agilent Technologies, Inc. as the real-party-in-interest. App. Br. 3.

STATEMENT OF THE CASE

Claims 1–5, 9–11, 13, 14, 16, 18, and 23² stand finally rejected by the Examiner as unpatentable. The rejections are as follows:

1. Claims 1–3, 5, 9, and 10 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Ehrlich et al. (US 2007/0087358 A1, published on April 19, 2007) (“Ehrlich”), Fresco et al. (US 2002/0137919 A1, published on September 26, 2002) and Nusbaum (US 6,013,435, published on January 11, 2000). Ans. 2–3.

2. Claims 1–3, 5, and 11 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Ehrlich, Fresco, and Keith (US 5,366,877, published on November 22, 1994). Ans. 5.

3. Claims 1–3, 5, and 13 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Ehrlich, Fresco, and Fu et al. (US 2013/0116130 A1, filed on December 15, 2011) (“Fu”). Ans. 8.

4. Claim 4 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Ehrlich, Fresco, and Nusbaum, Keith, or Fu, and further in view of Lao et al. (US 2009/0291475 A1, published on November 26, 2009) (“Lao”). Ans. 10.

5. Claim 23 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Ehrlich, Fresco, and Nusbaum, Keith, or Fu, and further in view of Peter et al. (US 2010/0330556 A1, published on December 30, 2010) (“Peter”). Ans. 12.

6. Claims 14, 16, and 18 are rejected under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which the

² The Final Office Action and the Appeal Brief listed additional claims as have been rejected for which no rejection appeared in the Answer.

inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Ans. 2.

Claim 1, the only independent claim on review, is reproduced below:

1. A method comprising:

a) clamping the top and bottom strands of a double stranded DNA molecule to produce a duplex in which the top and bottom strands are linked;

b) denaturing the duplex to produce a denatured product;
and

c) renaturing the denatured product in the presence of a labeled oligonucleotide,

wherein the labeled oligonucleotide hybridizes to a sequence of nucleotides on one strand in the double stranded DNA molecule, thereby producing a renatured, double-stranded product that comprises a triplex region comprising the labeled oligonucleotide.

OBVIOUSNESS REJECTIONS

Appellants traverse all the obviousness rejections together. Appeal Br. 5. The only claim addressed is independent claim 1, which is the only independent claim on appeal. We therefore focus our discussion on claim 1.

The Examiner found that Ehrlich describes the a) clamping, b) denaturing, and c) renaturing steps of claim 1 in the presence of an oligonucleotide. Ans. 3. Although the Examiner found that Ehrlich does not teach that a triplex region is produced comprising the oligonucleotide as required by claim 1, the Examiner found that Fresco teaches that a “triplex can be formed from a target duplex which comprises a single strand which hybridizes to itself via a hairpin turn, and a third strand probe.” *Id.* The Examiner further cited Nusbaum for teaching a labeled oligonucleotide and explained why one of ordinary skill in the art would have had reason to use labeled oligonucleotide in Ehrlich’s method to have arrived at the claimed

invention (“renaturing the denatured product in the presence of a labeled oligonucleotide”). *Id.* at 4.

Appellants contend that the Examiner erred in making the rejection.

Appellants contend that Ehrlich’s method would not result in renatured product as required by step c) of claim 1.

First, Appellants contend that Ehrlich treats the DNA with bisulfite which converts C’s to U’s and the resulting DNA would not contain enough G-C base pairs to renature to form double-stranded DNA. Appeal Br. 6. Appellants state that this argument is consistent with Ehrlich’s Figure 1A which shows which shows the DNA in an “open” configuration with unpaired bases. *Id.* A portion of Figure 1A from Ehrlich is reproduced below:

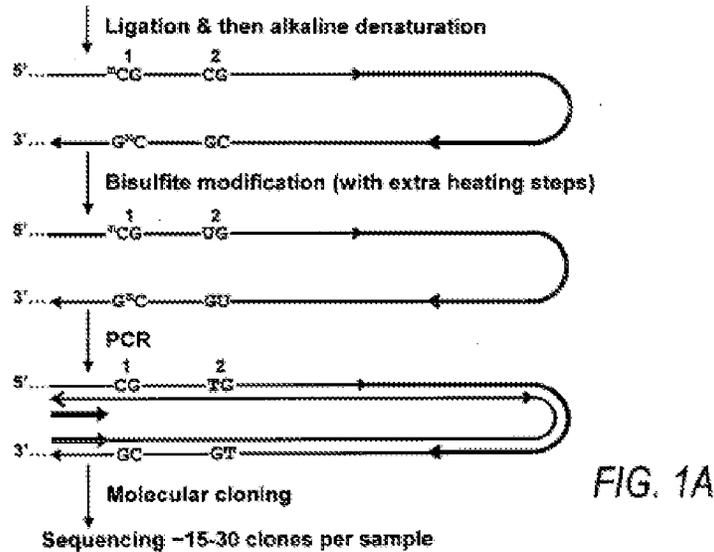


Figure 1A of Ehrlich shows that the DNA is denatured (“alkaline denaturation”) and then is subsequently treated with bisulfite (“Bisulfite modification”). After bisulfite modification, Ehrlich shows the DNA as

single-stranded and in an “open” configuration (middle drawing). Only after the “PCR” step does Ehrlich show the DNA as double-stranded again.

Second, Appellants provided drawings made using a secondary structure predictor said to demonstrate that Ehrlich’s method would result in DNA in the open single-stranded configuration and not a renatured product as required by the claim. Appeal Br. 7.

Third, Appellants cite a publication³ said to show that bisulfite treatment produces single-stranded DNA. Appeal Br. 7. Appellants quoted from page 1 of the publication as follows”

“This chemical treatment [i.e., bisulfite treatment] introduces various DNA strand breaks and results in highly fragmented *single-stranded* DNA” (emphasis added: language in brackets added by Appellant).

Appeal Br. 7.

In response, the Examiner stated that Appellants “has no evidence” to show that Ehrlich’s DNA would not contain enough G-C base pairs to form a double-stranded renatured target as required by step (c) of the claim. Ans. 17–18. This is not correct. As explained above, Appellants provided three lines of evidence to show that Ehrlich does not meet the step of claim 1 of “producing a renatured, double-stranded product.” Appeal Br. 6–7.

With respect to Ehrlich (2007), Appellants argue that the effect is due to urea and nothing to do with the bisulfite treatment. Appeal Br. 18. We agree with Appellants that evidence in Ehrlich (2007) is not persuasive because urea is also present in the reaction mixture and thus the conditions are not the same as Ehrlich.

³ Ehrlich et al., 2007, *Nucleic Acid Research*, 35(5):1–8 (e29) (“Ehrlich (2007)”).

The Examiner did not adequately address Appellants' argument regarding Fig. 1A of Ehrlich which shows a single-stranded DNA prior to the PCR reaction and after "Bisulfite modification," and not a renatured double-stranded product as required by the claim. The Examiner also did not address Appellants' reference to the secondary structure predictor as evidence that a double-stranded product would not form. Appeal Br. 7.

The Examiner extensively quoted from Appellants' brief (Ans. 16, 17, 19), including Appellants' reference to Figure 1A, but did explain how the single-stranded DNA shown in Figure 1A after "Bisulfite modification" would result in a "renatured, double-stranded product that comprises a triplex region" as recited in the claim. In the following step shown in Figure 1A, a double-stranded product is shown, but this is produced by extending the primers.

With regard to the limitation in the claim that a triplex region is formed in Ehrlich, the Examiner found that while Ehrlich is silent on this limitation, its method would inherently produce a triplex when a sample is treated with bisulfite and PCR is performed using PCR primers (i.e., the labeled oligonucleotide of claim 1). *See Ehrlich* ¶ 99.

It is well-established by precedent that when inherency is the basis of a rejection, the Examiner must have a "sound basis" for believing that a process carried out in the prior art produces the same result as claimed. *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990). The burden is properly shifted to a patent applicant when the Examiner establish a sound, factual basis to believe that a skilled artisan would have made substantially identical products from the teachings of the prior art. *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977).

In this case, Fresco indicates that there are specific ionic conditions for triplex formation. Fresco ¶ 19. The Examiner did not establish that such conditions would be present when Ehrlich's process is carried out. In addition, and independently, as discussed above, the Examiner also did not establish that a renatured product is formed as required by step c) of claim 1. Consequently, the Examiner did not provide adequate evidence that Ehrlich would have inherently formed a triplex region as required by all the claims.

For the foregoing reasons, the rejection of claim 1, and dependent claims 2–5, 9–11, 13, and 23 are reversed.

§ 112 REJECTION

Claim 14 depends from claim 9, which in turn depends from claim 1. Claim 14 further comprises step d) which recites “contacting the renatured product with a solid support comprising a surface tethered capture agent for the affinity tag.” Claim 1 recites that its process results in “a renatured, double-stranded product.” The Examiner rejected claim 14 “as vague and indefinite because it is unclear that ‘the renatured product’ recited in the claim is identical to a renatured, double-stranded product in claim 1 or not.” Final Act. 4.

The rejection of claim 14 is reversed. It is clear that “the” renatured product of claim 14 corresponds to the only “renatured product” recited in the chain of claims. The Examiner did not identify what is indefinite about the claim when claim 14 refers to “the” renatured product and claim 1 produces a renatured product, the only recited renatured product.

Claim 16 depends from claim 14 and further recites that “the method comprises supercoiling the renatured product after it is contacted with the

solid support.” The Examiner rejected the claim as indefinite because “the claim does not require that the renatured product has a closed circular DNA or a topologically distinct domain after it is contacted with the solid support, it is unclear why the renatured product can be supercoiled.” Final Act. 4.

The claim language that the method “comprises supercoiling the renatured product” is a functional limitation because it does not recite how the supercoiling is accomplished. A functional limitation does not necessarily mean that a claim is indefinite.

A patent applicant is free to recite features of an apparatus either structurally or functionally. *See In re Swinehart*, 439 F.2d 210, 212 . . . (CCPA 1971) (“[T]here is nothing intrinsically wrong with [defining something by what it does rather than what it is] in drafting patent claims.”). *In re Schreiber*, 128 F.3d 1473, 1478 (Fed. Cir. 1997) (alteration in original).

The Examiner did not dispute that it was known how to achieve supercoiling. As indicated by the Examiner, supercoiling is accomplished when both ends of the DNA are closed. Claim 1 requires that one end of the double-stranded DNA is clamped, linking the DNA strands together. With regard to creating a closed DNA from the clamped DNA, the Specification describes one embodiment in which supercoiling is achieved by using a bidentate capture oligo to create a closed domain that can be supercoiled. Spec. 19:11–20:8. Thus, we do not agree with the Examiner that the claim is indefinite. The rejection of claim 16 is reversed.

Claim 18 depends from claim 2, which depends from claim 1. Claim 2 further recites covalently linking the clamped strands. Claim 18 recites where the “covalently linking is done by ligating a hairpin adaptor to the double stranded DNA and wherein the hairpin adaptor comprises a

nucleotide sequence that produces a restriction site if an adaptor dimer is produced.”

The Examiner rejected the claim as vague and indefinite because “the first part of the claim only requires one hairpin adaptor while the second part of the claim requires an adaptor dimers are produced, it is unclear what forms an adaptor dimers.” Final Act. 5. The Examiner also states that the claim is indefinite because “the claim does not describe what kind of specific structure the hairpin adaptor has, it is unclear why ligating a hairpin adaptor to the double stranded DNA must form an adaptor dimers and cannot form an adaptor monomer.” *Id.*

We do not agree with the Examiner that the claim is indefinite. The Specification defines a hairpin adapter as “one molecule that base pairs with itself to form a structure that has a double stranded stem and a loop, where the 3' and 5' ends of the molecule ligate to the 5' and 3' ends of the double stranded DNA molecule, respectively.” Spec. 11:18–21. The Specification also describes that when two hairpins ligate together to form an “adapter dimer,” a restriction site is generated that can be cut by a restriction enzyme. *Id.* at 17:22–25; Fig. 9. Thus, the claim, when read in light of the Specification, would be understood by one of ordinary skill in the art. The rejection of claim 18 is reversed.

For the foregoing reason, the indefiniteness rejection of claims 14, 16, and 18 are reversed.

REVERSED