

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ENVIROLOGIX INC.,  
Petitioner,  
v.

IONIAN TECHNOLOGIES, INC.,  
Patent Owner.

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Case IPR2018-00406  
Patent 9,562,264 B2

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Before ULRIKE W. JENKS, CHRISTOPHER G. PAULRAJ, and  
ROBERT A. POLLOCK, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge*.

DECISION

Denying Institution of *Inter Partes* Review  
*37 C.F.R. § 42.108*

## I. INTRODUCTION

EnviroLogix Inc. (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1–6 and 8–29 of U.S. Patent No. 9,562,264 B2 (Ex. 1001, “the ’264 patent”). Paper 1 (“Pet.”). Ionian Technologies, Inc (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 10 (“Prelim. Resp.”).

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the Petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Upon consideration of the arguments and evidence presented in the Petition and the Preliminary Response, we are not persuaded that Petitioner has established a reasonable likelihood that it would prevail in its challenges to claims 1–6 and 8–29 of the ’264 patent. Accordingly, we do not institute an *inter partes* review of claims 1–6 and 8–29.

## II. BACKGROUND

### A. *Related Proceedings*

Petitioner identifies as related matters three patents U.S. Patent No. 9,562,263 B2 (“the ’263 patent”), U.S. Patent No. 9,617,586 B2 (“the ’586 patent”), U.S. Patent No. 9,689,031 B2 (“the ’031 patent”). Pet. 2 (“Petitioner reserves the right to petition for *inter partes* review of 9,562,263, 9,617,586 and 9,689,031”). The claims in the ’263 patent are directed to a method of amplifying a target polynucleotide. We note that Petitioner has filed a request for *inter partes* review in the ’263 patent. *See* IPR2018-00405. Concurrently herewith, we issue also a decision in that related proceeding.

*B. The '264 Patent (Ex. 1001)*

The '264 patent issued from Application No. 14/067,623 (“the '623 application”), filed October 30, 2013, now U.S. Patent No. 9,562,264 B2; which is a continuation of Application No. 11/778,018, filed July 14, 2007.

The '263 patent relates to amplification of nucleic acid targets using a nicking enzyme. A nicking enzyme amplification reaction (NEAR) requires the presence of (1) a nucleic acid target, (2) at least two template oligonucleotides, (3) a thermophilic nicking enzyme, (4) a thermophilic polymerase, and (5) buffer components all held at the reaction temperature. Ex. 1001, 18:46–49.

The '264 patent provides that when using “a double-stranded target, both templates can interact with the corresponding target strands simultaneously.” *Id.* 18:60–61. “The double-strand formed from the extension of both templates creates a nicking enzyme binding site on either end of the duplex. This double-strand is termed the NEAR amplification duplex.” *Id.* 19:27–31. The NEAR amplification method “do[es] not require the use of temperature cycling, as often is required in methods of amplification to dissociate the target sequence from the amplified nucleic acid.” *Id.* 19:63–66. The '263 patent provides that even though temperature cycling is not required, the temperature should be high enough to minimize nonspecific binding. *Id.* 20:2–3. “The polymerase may be mixed with the target nucleic acid molecule before, after, or at the same time as, the nicking enzyme.” *Id.* 20:9–11. “The reaction is run at a constant temperature, usually between 54° C. and 60° C. for the enzyme combination of Bst polymerase (large fragment) and Nt.Bst.NB1 nicking enzyme.” *Id.* 21:28–31. The product of the NEAR amplification can be visualized by gel

electrophoresis or mass spectroscopy. *Id.* 26:24–25, 64–66. Alternatively, the product can be detected in real-time using SYBR II fluorescence (*id.* 27:16–17), Fluorescence Resonance Energy Transfer (FRET) (*id.* at 27:31–32), or using molecular beacons. *Id.* at 27:48–49.

*C. Illustrative Claim*

Claim 1, the sole independent claim of the '264 patent is illustrative and reproduced below:

1. A method of amplifying a target polynucleotide sequence, the method comprising:
  - (a) obtaining, from an animal, a sample comprising a target nucleic acid, the target nucleic acid comprising the target polynucleotide sequence,
  - (b) without first subjecting the target nucleic acid to a thermal denaturation step associated with amplification of the target polynucleotide sequence, combining, in a single step, the obtained sample directly with an amplification reagent mixture or diluting the obtained sample and combining, in a single step, the diluted sample with an amplification reagent mixture, in either case, the amplification reagent mixture being free of bumper primers and comprising:
    - (i) a polymerase,
    - (ii) a nicking enzyme,
    - (iii) a first oligonucleotide comprising a 5' portion that comprises a nicking enzyme binding site that is non-complementary to the target polynucleotide sequence and a 3' portion that hybridizes to the target polynucleotide sequence, and
    - (iv) a second oligonucleotide comprising a 5' portion that comprises a nicking enzyme binding site that is non-complementary to the target polynucleotide sequence and a 3' portion that hybridizes to the target polynucleotide sequence,
  - (c) amplifying the target polynucleotide sequence, without the assistance of bumper primers, by subjecting the reaction

mixture formed by the step of combining to essentially isothermal conditions, from steps comprising:

- (i) forming a first duplex comprising the target polynucleotide sequence and the first oligonucleotide;
  - (ii) extending, using the polymerase, the first oligonucleotide along the target polynucleotide sequence to form an extended first oligonucleotide comprising a sequence complementary to the second oligonucleotide;
  - (iii) forming a second duplex comprising the second oligonucleotide and the extended first oligonucleotide;
  - (iv) extending, using the polymerase, the second oligonucleotide along the extended first oligonucleotide to form a third duplex comprising an extended second oligonucleotide comprising a sequence complementary to the first oligonucleotide and a first double-stranded nicking enzyme binding site;
  - (v) nicking, with the nicking enzyme, the first nicking site on the third duplex to produce a fourth duplex comprising the extended second oligonucleotide and a fragment of the extended first oligonucleotide; and
  - (vi) extending, using the polymerase, the fragment of the extended first oligonucleotide along the extended second oligonucleotide of the fourth duplex to produce a double-stranded nucleic acid product containing a second double-stranded nicking enzyme binding site, and
- (d) detecting the amplified target polynucleotide sequence in real time within 10 minutes of subjecting the reaction mixture to essentially isothermal conditions.

Ex. 1001, 32:18 to 33:8 (formatting added).

*D. Prior Art*

Petitioner relies upon the following prior art references:

Ehses et al. ("Ehses")	<i>Optimization and design of oligonucleotide setup for strand displacement amplification</i> , 63 J. BIOCHEM. BIOPHYS. METHODS 170–186 (2005).	Ex. 1002
Ehses ("Ehses Dissertation")	<i>Isothermale in vitro Selektion und Amplifikation zur Untersuchung von Evolutionsvorgängen</i> , Dissertation (2005).	Ex. 1003
Ehses (Dissertation Translation")	<i>Isothermal In Vitro Selection and Amplification to Investigate Evolutionary Processes</i> .	Ex. 1004
Piepenburg et al. ("Piepenburg")	US 2005/0112631 A1, publ. May 26, 2005.	Ex. 1005
Kong et al. ("Kong")	WO 01/94544 A2, publ. Dec. 13, 2001.	Ex. 1006
Kato and Kuramitsu ("Kato")	<i>Characterization of thermostable RecA protein and analysis of its interaction with single-stranded DNA</i> , 259 FEBS Journal 592–601 (1999).	Ex. 1007

Petitioner also relies upon the Declaration of Dr. Jeremy Edwards.  
 (Ex. 1008).

*E. Asserted Grounds of Unpatentability*

Petitioner challenges the patentability of claims 1–6 and 8–29 of the '264 patent on the following grounds (Pet. 3):

Claims Challenged	Basis	References
1–4, 6, 8–11, 13, and 15–29	§ 102(b)	Ehses

<b>Claims Challenged</b>	<b>Basis</b>	<b>References</b>
1–4, 6, 8–11, 13, and 15–29	§ 102(b)	Ehse-Dissertation
1–4, 6, 8–11, 13, and 15–29	§ 103(a)	Ehse and Ehse-Dissertation
1–6, 8–14, 16, and 19–29	§ 102(b)	Piepenburg
15	§ 103(a)	Piepenburg in view of Kong
17	§ 103(a)	Piepenburg in view of Kato
1–6 and 8–29	§ 103(a)	Piepenburg in view of Ehse and Ehse Dissertation
1–6 and 8–29	§ 103(a)	Ehse and Ehse Dissertation in view of Piepenburg

### III. ANALYSIS

#### A. *Claim Construction*

Petitioner includes a claim construction section for numerous claim terms or phrases that appear in the claims. Pet. 8–13. Patent Owner’s position is that no claim terms require construction at this stage of the proceeding. Prelim. Resp. 2. On this record, we determine that no claim term requires express construction for the purpose of rendering this decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (“[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.”).

#### B. *Level of Skill in the Art*

Petitioner contends that person of ordinary skill in the art (“POSITA”) would have “knowledge of molecular biology, a Ph.D. in molecular biology, and experience in nucleic acid amplification techniques, detection, and analysis.” Pet. 5. Patent Owner does not address the level of skill in the art

in its preliminary response. For purposes of this decision, we find Petitioner's requirements for the POSITA to be reasonable and apply that skill level for our analysis.

*C. Anticipation by Ehses (Ex. 1002)*

*1. Overview of Ehses*

Ehses is a journal article, published in May 2005, which is directed to optimizing strand displacement amplification (SDA). Ex. 1002, Abstract. SDA is an all-purpose DNA amplification reaction that works in isothermal conditions. Ex. 1002, Abstract, *see id.* at 171 (SDA method is "a sensitive and universal tool for amplification of nucleic acids"). According to Ehses, the problem with isothermal amplification mechanisms is the accumulation of unpredictable byproduct. *Id.*, Abstract.

Ehses teaches optimizing oligonucleotides for SDA. Ex. 1002, Title. Ehses's test system contains only the essential components for the SDA reaction: DNA, primer, enzymes, buffer. *Id.* at 175. "[T]he primer consists of a 5' overlapping end following the recognition site of the restriction enzyme and a template-binding region on its 3' end." *Id.* at 173. The standard SDA protocol and nicking-SDA protocol described in Ehses both dilute primers in buffer and add template DNA, before incubating this mixture for

3 min at 95°C followed by 1 min at 55°C. Upon addition of the enzymes, the amplification mixture was incubated 15–60 min in an ICycler (BioRAD) and the increase in fluorescence intensity was monitored. The reaction was stopped by addition of denaturing Stop/Loading dye and products were denatured at 95°C for 10 min. Aliquots of 10 µl from each sample were added to 5 µl of the loading dye and analyzed by 12% denaturing polyacrylamide gel electrophoresis, with subsequent staining via

SYBR Gold or SYBR Green II and visualization under UV illumination.

*Id.* at 175. “When performing the standard reaction . . . the expected products were achieved with amplification starting with template concentrations of 10 and 100 pM in 20 min for SDA and nicking SDA respectively.” *Id.* at 177. “When starting with less template, omitting the initial denaturation step or increasing the reaction time, the standard SDA system as well as the nicking system shows the tendency to [develop] side-reactions.” *Id.* at 177. “When using an intercalating fluorescence dye TOPRO-1 in real-time detection, after about 20 min the fluorescence intensity signal shows a steep increase (results not shown).” *Id.* at 178.

## 2. *Analysis*

Petitioner contends that claims 1–4, 6, 8–11, 13, and 15–29 are anticipated by Ehses. Pet. 13–27. We focus our analysis on certain limitations of independent claim 1 as they are dispositive to our conclusion for all the challenged claims.

Petitioner asserts that Ehses’s disclosed AmpRxn protocol (a variation of SDA) is a method of amplifying a target polynucleotide. Pet. 15 (citing Ex. 1008 ¶ 33). According to Petitioner, because Ehses discloses that SDA amplification is valuable for DNA diagnostics, a POSITA would understand that the diagnostic applications include the analysis of polynucleotide samples derived from animals. *Id.* (citing Ex. 1008 ¶ 33; Ex. 1002, 171). With respect to the claim limitation “without first subjecting the target nucleic acid to a thermal denaturation step associated with amplification of the target polynucleotide sequence,” Petitioner asserts that Ehses’s disclosure of “*omitting the initial denaturation step*” demonstrates that

“thermal denaturation is **not** required for amplification of a Target.” *Id.* at 15–16 (citing Ex. 1008 ¶ 35; Ex. 1002, 177). Additionally, with respect to the requirement of “combining in a single step” the sample with an amplification reagent mixture that is “free of bumper primers,” Petitioner contends that “[b]ecause thermal denaturation is not required, the sample and AmpRxn components are combined and incubated in a single step.” *Id.* (citing Ex. 1008 ¶ 37). Petitioner also contends that the SDA protocol “includes a pair of primers for amplifying a sample, but does not include or require bumper primers for amplification.” *Id.* at 17 (citing Ex. 1008 ¶¶ 38–39). Petitioner notes that the Ehses amplification reagent comprises a polymerase, a nicking enzyme, and a first and second oligonucleotide. *Id.* at 17–19. According to Petitioner, Ehses’s SDA reaction protocol “does not require an initial denaturation step, but is performed under isothermal conditions, i.e., at 55 °C.” *Id.* at 19 (citing Ex. 1002, 173, 175, 177).

Petitioner contends that Ehses discloses detecting amplification of the Target in real time (RT), and further asserts that “[g]iven that the reaction [in Ehses] is monitored throughout the incubation, the presence of amplification product is detected as it accumulates.” *Id.* at 21–22. Specifically, Petitioner directs our attention to the incubation times of essays that indicates an incubation time varying from 15 to 60 minutes. *Id.* at 22 (citing Ex. 1002, 175, citing Ex. 1008 ¶ 51 (“Given that nSDA is performed using the same components and under the same conditions as the claimed method, a POSA understands that the time to detection would necessarily be the same”)), *see also* Pet. 26 (citing Ex. 1008 ¶ 74). Petitioner also relies upon its declarant Dr. Edwards’ assertion that “[d]yes that bind DNA, like TO-PRO-1,

generate a fluorescent signal upon binding that is detected in RT.” *Id.* at 21 (citing Ex. 1008 ¶ 49).

Patent Owner responds that Ehses does not expressly teach the following claim requirements: (1) a DNA sample derived from an animal, (2) a reaction that omits a denaturation step and still detects target DNA, (3) a single step reaction, and (4) and detection of the product within 10 minutes. *See* Prelim. Resp. 5–12. For the reasons set out below, we agree with Patent Owner that Petitioner has not shown, on this record, a reasonable likelihood of establishing that any of the challenged claims are anticipated by Ehses. In particular, we determine that Petitioner has not shown that Ehses teaches at least the claim requirements of omitting a thermal denaturation step and detecting the amplified product within 10 minutes after subjecting the reaction mixture to essentially isothermal conditions.

With respect to the requirement that thermal denaturation is omitted, Patent Owner argues that “[t]he sentence of Ehses upon which Petitioner relies for disclosure of omitting an initial denaturation step expressly teaches the reader *not* to omit an initial denaturation step—because doing so ‘shows the tendency to side-reactions.’” Prelim. Resp. 7 (citing Ex. 1002, 177). Ehses discloses that undesirable side-reactions results in DNA product that is not detectable, for example with staining. *See* Ex. 1002, Fig. 3 C (“Comparative product analysis after 90 min reaction time at 55°C. . . . Because of the increased side-reactions, the desired product cannot be detected by subsequent staining with SYBR Gold”). Ehses teaches other sample handling conditions also result in undesirable side reactions, such as for example omitting the denaturation step. *Id.* at 177 (“When starting with less template, omitting the initial denaturation step or increasing the reaction

time, the standard SDA system as well as the nicking system shows the tendency to side-reactions”). Thus, although Ehses might disclose a methodology that omits the initial thermal denaturation step, Petitioner has not shown that this method results in a detectable product. *See id.* The claims, however, require amplifying the target sequence such that the amplified target polynucleotide sequence is detectable. Therefore, we agree with the Patent Owner that there is insufficient evidence, on this record, to show that a target product would be detectable when the thermal denaturation step is omitted as taught by Ehses.

With respect to the requirement of detecting in real time the amplified product within 10 minutes, Patent Owner argues:

Ehses does not disclose any results of amplification reactions in which target DNA was detected within ten minutes—nor does Ehses state that its amplification reactions are capable of producing detectable target within ten minutes. In fact, both of the SDA protocols that Ehses discloses require incubation with DNA polymerase for a minimum of 15 minutes.

Prelim. Resp. 10. We agree with the Patent Owner that Petitioner presents insufficient evidence showing that Ehses discloses that the desirable product can be detected before a minimum 15 minute time interval. In both the SDA and nicking SDA reactions described in Ehses, the amplification mixture Ehses was “incubated 15–60 [minutes] . . . and the increase in fluorescence intensity was monitored. The reaction was stopped by addition of denaturing Stop/Loading dye and products were denatured at 95°C for 10 [minutes].” Ex. 1002, 175. Following the standard procedure outlined in Ehses, the detection of product took minimally a 15 minute incubation in addition to a 10 minute denaturation step before the product is finally detected on the gel. *See id.* The reaction can proceed as long as 60 minutes.

*See id.* Ehses also discloses the use of real-time detection, but indicates that fluorescence intensity increases after 20 minutes. *See id.* at 178 (“An indication of the amplification of non-specific products is also given by a two step kinetic profile. When using an intercalating fluorescence dye TOPRO-1 in real-time detection, after about 20 min the fluorescence intensity signal shows a steep increase”). Thus, the Ehses reference itself indicates that using real-time detection based on fluorescence intensity Ehses will take longer than 10 minutes.

In sum, we agree with Patent Owner that the record does not show that Ehses discloses a procedure that omits the denaturation step for the amplification of target DNA, and achieving target detection within 10 minutes as claimed. Accordingly, we decline to institute *inter partes* review Ehses based on this ground.

*D. Anticipation by Ehses Dissertation (Ex. 1003/Ex. 1004)*

Petitioner also asserts that claims 1–4, 6, 8–11, 13, and 15–29 are anticipated by the Ehses Dissertation. Pet. 27–38. Petitioner asserts that “Ehses-Dissertation<sup>1</sup> is prior art to the ’264 patent under 35 U.S.C. §102(b) (pre-AIA) because it was published on August 7, 2005.” *Id.* at 27.

Petitioner relies upon the date of oral examination identified in the Ehses Dissertation as the date of publication. Ex. 1004, 3. Patent Owner opposes Petitioner’s assertions because, *inter alia*, the Petition fails to show that the Ehses Dissertation qualifies as a “printed publication.” Prelim. Resp. 12.

We agree with Patent Owner that Petitioner has not met its burden of

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<sup>1</sup> Petitioner provides a copy of Ehses Dissertation written in German (Ex. 1003); all references to the Ehses Dissertation in this decision are made in reference to the English translation submitted as Exhibit 1004.

establishing that the Ehses Dissertation qualifies as prior art. As such, we do not address the technical merits of Petitioner's anticipation challenge based on the Ehses Dissertation.

A party seeking to introduce a reference “should produce sufficient proof of its dissemination or that it has otherwise been available and accessible to persons concerned with the art to which the document relates and thus most likely to avail themselves of its contents.” *In re Wyer*, 655 F.2d 221, 227 (CCPA 1981) (quoting *Philips Elec. & Pharm. Indus. Corp. v. Thermal & Elecs. Indus., Inc.*, 450 F.2d 1164, 1171 (3d Cir. 1971)). The determination of whether a given reference qualifies as a prior art “printed publication” involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public. *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004). “Because there are many ways in which a reference may be disseminated to the interested public, ‘public accessibility’ has been called the touchstone in determining whether a reference constitutes a ‘printed publication’ bar under 35 U.S.C. § 102(b).” *In re Hall*, 781 F.2d 897, 898–99 (Fed. Cir. 1986). To qualify as a prior art printed publication, the reference must have been disseminated or otherwise made accessible to persons interested and ordinarily skilled in the subject matter to which the document relates prior to the critical date. *Kyocera Wireless Corp. v. Int'l Trade Comm'n*, 545 F.3d 1340, 1350 (Fed. Cir. 2008).

Upon consideration of the facts in the present record, we agree with Patent Owner's contention that Petitioner's reliance on the disclosure of the date of an oral dissertation defense is not sufficient to establish that the dissertation was made publicly available at that time. *See generally* Prelim.

Resp. 12–16; *see also id.* at 14 (“the date of the author’s oral examination does not establish when the dissertation became accessible to the public”). Absent in the Petition is evidence related to whether the Eshes Dissertation was publicly accessible in the relevant time frame, how one might have obtained a copy of the dissertation, or whether the dissertation was reasonably accessible through generally available means, or by a showing of general library procedure as to indexing, cataloging, and shelving of doctoral thesis. We acknowledge that Petitioner may rely on evidence of routine business practices, such as by a showing of general library procedure as to indexing, cataloging, and shelving of doctoral thesis, and that Petitioner does not have to show a specific date on which Eshes Dissertation was publicly accessible. *See Hall*, 781 F.2d at 899. Here, though, Petitioner does not submit evidence from which we can even approximate when Eshes Dissertation became publicly accessible. We agree with Patent Owner that “[w]ithout more here, [the] contentions and evidence cited by Petitioner do not rise to the level of ‘threshold evidence’ that justifies going forward with a trial on any ground that relies on the [Eshes–Dissertation] as ‘printed publication’ prior art.” *See* Prelim. Resp. 16 (citing *Seabery North America, Inc. v. Lincoln Global, Inc.*, IPR2016-00904, Paper 12 at 7-8 (PTAB Nov. 3, 2016)).

Because we are not persuaded that Petitioner has made a threshold showing that the Eshes Dissertation was sufficiently publicly accessible to qualify as a “printed publication” under § 102(b), we also decline to institute *inter partes* review based on this ground.

*E. Anticipation by Piepenburg (Ex. 1005)*

*1. Overview of Piepenburg*

Piepenburg is a U.S. Patent Application published May 26, 2005. Ex. 1005. Piepenburg describes several methods for recombination polymerase amplification (RPA) of target DNA. Ex. 1005, Abstract, ¶ 371. As explained in Piepenburg, “an RPA reaction may be used to determine the presence or absences of a nucleic acid molecule,” where “[t]he nucleic acid molecule may be from any organism.” *Id.* ¶ 223. Piepenburg’s amplification methods “avoid any requirement for thermal melting of DNA thermostable components.” *Id.* ¶ 12.

The method [of Piepenburg] comprises two steps. In the first step, the following reagents are combined in a reaction: (1) at least one recombinase; (2) at least one single stranded DNA binding protein; (3) at least one DNA polymerase; (4) dNTPs or a mixture of dNTPs and ddNTPs; (5) a crowding agent; (6) a buffer; (7) a reducing agent; (8) ATP or ATP analog; (9) at least one recombinase loading protein; (10) a first primer and optionally a second primer; and (11) a target nucleic acid molecule. In the second step, the reagents are incubated until a desired degree of amplification is achieved.

*Id.* ¶ 69. “The reaction may be incubated between 5 minutes and 16 hours, such as between 15 minutes and 3 hours or between 30 minutes and 2 hours. The incubation may be performed until a desired degree of amplification is achieved.” *Id.* ¶ 91, *see also id.* ¶ 499 (“Using optimally short target sequences and sensitive detection method, we expect that a diagnostic amplification/detection assay could be performed within an hour”). Piepenburg discloses “[d]etection may be performed using any method, such as, for example, using electrophoresis on an agarose or PAGE gel followed by ethidium bromide staining.” *Id.* ¶ 101, *see also id.* ¶ 157 (The use of

“[l]abeled primers offer the advantage of a more rapid detection of amplified product”). “RPA is initiated by targeting sequences using synthetic oligonucleotides coated with RecA, or a functional homologue.” *Id.* ¶ 121.

Figure 11 of Piepenburg, reproduced below, shows uses of backfire RPA priming reaction.

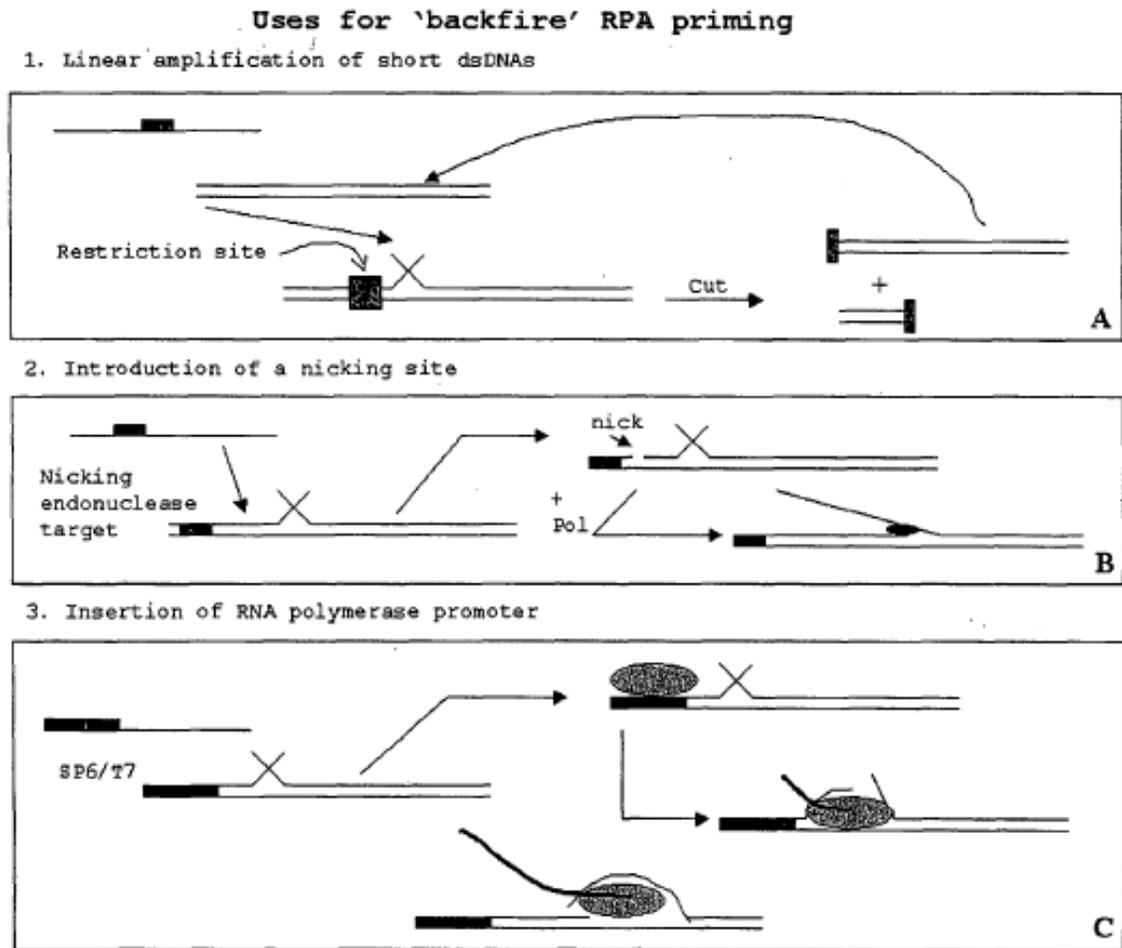


Figure 11

As depicted in the figure above, examples of backfire priming include the “introduction of a nicking enzyme target site, introduction of an RNA polymerase promoter, and the linear generation of short dsDNA fragments through successive invasion/synthesis/cleavage events.” *Id.* ¶ 29, *see id.* ¶¶

411–412. “Backfire synthesis occurs when a recombinase-coated targeting oligonucleotide possessing a 5’ overhang invades a duplex DNA end in the presence of a suitable polymerase and dNTPs.” *Id.* ¶ 408. “[T]he 5’ overhang of a targeting oligonucleotide is designed such that should backfire synthesis occur, a target for a nicking endonuclease is generated.” *Id.* ¶ 412. In the presence of a nicking endonuclease and suitable polymerase, extension of the nick and displacement of DNA strand occurs. *See id.* “Multiple strands may be run-off by successive nicking and elongation from a single template.” *Id.*

## 2. Analysis

Petitioner assert that claims 1–6, 8–14, 16, and 19–29 of the ’264 patent are anticipated by Piepenburg. Pet. 40–53. We again focus our analysis on certain limitations of independent claim 1 as they are dispositive to our conclusion for all the challenged claims.

With respect to the claim requirements of a “first oligonucleotide” and “second oligonucleotide” having “a 5’ portion that comprises a nicking enzyme binding site that is noncomplementary to the target polynucleotide sequence and a 3’ portion that hybridizes to the target polynucleotide sequence,” Petitioner contends that Piepenburg discloses the requisite first and second oligonucleotides. *Id.* at 46–47 (citing Ex. 1005 ¶¶ 29, 412, Fig. 11B; Ex. 1008 ¶ 144).

Patent Owner responds that “neither paragraph of Piepenburg upon which Petitioner relies—nor Fig. 11B—discloses a second oligonucleotide of any kind.” Prelim. Resp. 28. We agree with Patent Owner. We do not glean any disclosure in the cited portions of Piepenburg of an amplification

reaction involving two separate oligonucleotides having the structure recited in claim limitations 1(b)(iii) and 1(b)(iv).

As a separate basis, we find that Petitioner has also not shown that Piepenburg discloses detecting in real time the amplified product within 10 minutes. Petitioner asserts that Piepenburg describes real-time detection of target. Pet. 49 (citing Ex. 1005 ¶ 203). Based on Piepenburg's disclosure that the reaction can be carried out between 5 minutes and 16 hours, Petitioner contends that "[t]he same components recited in the claims are present in the nicking enzyme-dependent strand-displacement amplification reactions of Piepenburg and are incubated under the same conditions," and "[a]ll else being equal, the AmpRxns of Piepenburg would necessarily achieve the same results as the claimed method in the same time frame under isothermal conditions." *Id.* at 50 (citing Ex. 1008 ¶ 52). As noted by Patent Owner, the disclosure relied upon by the Petitioner says nothing about detection and only refers to incubation. Prelim. Resp. 32 (citing Ex. 1005 ¶ 91 ("The incubation may be performed until a desired degree of amplification is achieved")). Although Piepenburg discloses incubation times that range from 5 minutes to 16 hours, we agree with Patent Owner that the evidence of record is insufficient to establish that an incubation time of 5 minutes would provide sufficient detectable product, especially when the working examples "exclusively refers to reaction incubation times on the order of an hour or more." *Id.* at 33. We further agree with Patent Owner that teaching an incubation time of as little as 5 minutes in conjunction with the generic teaching "until a desired degree of amplification is achieved" is not sufficient to show that amplification for 5 minutes is sufficient to detect the product "in real time within 10 minutes" as claimed. *Id.* Anticipation by

inherency requires that any material missing from the prior art must necessarily be present and would be recognized as such by POSITA. *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999).

In sum, we agree with Patent Owner that the record does not show that Piepenburg discloses an amplification procedure that includes a “first oligonucleotide” and “second oligonucleotide,” and detecting the target in real time within 10 minutes as claimed. Accordingly, we decline to institute *inter partes* review based on this ground.

*F. Remaining Obviousness Grounds:*

1. *Obviousness over Ehses and Ehses Dissertation*
2. *Obviousness over Piepenburg and Kong (Ex. 1006)*
3. *Obviousness over Piepenburg and Kato (Ex. 1007)*
4. *Obviousness over Piepenburg in view of Ehses and Ehses Dissertation*
5. *Obviousness over Ehses and Ehses Dissertation in view of Piepenburg*

Petitioner includes several obviousness challenges as part of its Petition. In particular, Petitioner asserts that claims 1–4, 6, 8–11, 13, and 15–29 of the ’264 patent would have been obvious over the combination of Ehses and Ehses Dissertation. Pet. 39–40. Petitioner also asserts that claim 15 is rendered obvious by Piepenburg in view of Kong (*id.* at 54–55), that claim 17 is rendered obvious by Piepenburg in view of Kato (*id.* at 55–56), that claims 1-6 and 8–29 are rendered obvious by Piepenburg in view of Ehses and Ehses Dissertation (*id.* at 56–57), and that claims 1-6 and 8–29 are rendered obvious over Ehses and Ehses Dissertation in view of Piepenburg (*id.* at 57–58). Petitioner’s obviousness contentions do not remedy the deficiencies in Ehses, Ehses Dissertation, and Piepenburg noted above with respect to the anticipation grounds. Accordingly, we decline to

institute *inter partes* review based on the obviousness grounds set forth in the Petition.

#### IV. CONCLUSION

Taking account of the information presented in the Petition and the Preliminary Response, and the evidence of record, we determine that Petitioner fails to demonstrate a reasonable likelihood of prevailing at trial as to any challenged claim. Accordingly, the Petition is denied, and no trial is instituted.

#### V. ORDER

It is hereby

ORDERED that the Petition is *denied* as to all challenged claims of the '264 patent, and no trial is instituted.

Case IPR2018-00406  
Patent 9,562,264 B2

PETITIONER:

Jonathan D. Ball  
Melissa Hunter-Ensor  
GREENBERG TRAURIG, LLP  
ballj@gtlaw.com  
hunterensorm@gtlaw.com

PATENT OWNER:

Aaron F. Barkof  
Christopher P. Singer  
MCANDREWS, HELD & MALLOY, LTD.  
abarkoff@mcandrews-ip.com  
csinger@mcandrews-ip.com