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Paper 7
Date: April 25, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTEGRATED DNA TECHNOLOGIES, INC.,
Petitioner,

v.

TECAN GENOMICS, INC.,
Patent Owner.

IPR2025-00016
Patent 10,876,108 B2

Before GEORGIANNA W. BRADEN, ZHENYU YANG, and TIMOTHY G. MAJORS, *Administrative Patent Judges.*

YANG, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Integrated DNA Technologies, Inc. ("Petitioner") filed a Petition (Paper 1, "Pet."), seeking *inter partes* review of claims 1–3, 5–12, and 14–19 of U.S. Patent No. 10,876,108 B2 (Ex. 1002, "the '108 patent"). Tecan Genomics, Inc. ("Patent Owner") filed a Preliminary Response. Paper 6 ("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).

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). We decline to deny the Petition on the basis of discretion under § 325(d). We institute *inter partes* review of all challenged claims based on all the grounds raised in the Petition.

A. Real Parties in Interest

Petitioner identifies itself and Danaher Corporation as the real parties in interest for Petitioner. Pet. 72. Patent Owner identifies itself and Tecan Group AG (also known as Tecan Group Ltd.) as the real parties in interest for Patent Owner. Paper 3, 1.

B. Related Matters

The parties inform us that Patent Owner has asserted the '108 patent in *Tecan Genomics, Inc. v. Invitae Corp.*, Case No. 1:23-cv-01114 (D. Del.) and *Tecan Genomics, Inc. v. QIAGEN Sciences, LLC*, Case No. 1:23-cv-01115-GBW (D. Del.). Pet. 72; Paper 3, 1.

Petitioner concurrently filed IPR2025-00015 against U.S. Patent No. 10,036,012 ("the '012 patent"), which claims priority to the same provisional patent application as the '108 patent. Pet. 73; Paper 3, 1.

Patent Owner further represents that QIAGEN Sciences, LLC filed IPR2025-00028 and IPR2025-00029, challenging the '012 patent and the '108 patent, respectively. Paper 3, 1.

C. The '108 Patent

The '108 patent "provides methods, compositions and kits for targeted nucleic acid sequence enrichment in a nucleic acid sample and for high efficiency nucleic acid library generation for next generation sequencing (NGS)." Ex. 1002, Abstract; *see also id.* at 2:34–36 (disclosing "methods for enriching for target nucleic acid sequences of interest in a sample comprising nucleic acids").

The '108 patent states that, with the rapid development of NGS technologies and platforms, whole genome sequencing became more feasible and less expensive. Ex. 1002, 1:18–20. It was nonetheless "often more practical and cost-effective to select genomic regions of interest for sequencing and analysis." *Id.* at 1:27–29.

Target enrichment was commonly used in genomic DNA sequencing to selectively capture genomic regions of interest from a DNA sample before sequencing. *Id.* at 1:29–32. At the time of the '108 patent invention, there were three major categories of target enrichment methods, including PCR-based methods, capture-by-hybridization, i.e., on-array or in-solution hybrid capture methods, and capture-by-circularization, i.e., molecular inversion probe-based methods. *Id.* at 1:44–49. According to the '108 patent, each of these methods has its distinct advantages and disadvantages. *Id.* at 1:44–46.

The ’108 patent explains that “[t]here is a need for improved methods for selective target enrichment that allow for low-cost, high-throughput capture of genomic regions of interest without specialized instrumentation. Additionally, there is also a need for high efficiency nucleic acid library generation.” *Id.* at 2:27–31. The ’108 patent purports to address both of these needs. *Id.* at 2:31–32.

D. Illustrative Claim

Independent claim 1 is illustrative of the claimed subject matter and is reproduced below.

> 1. A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:
>
> a) annealing one or more oligonucleotides in solution in a reaction mixture to the nucleic acid sequence of interest in a nucleic acid fragment, wherein the reaction mixture comprises a plurality of nucleic acid fragments, wherein the nucleic acid fragment comprising the nucleic acid sequence of interest comprises a first adaptor sequence, wherein the one or more oligonucleotides comprise a 3′ portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest and a 5′ tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;
>
> b) extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragment comprising the first adaptor sequence with a polymerase, in the reaction mixture, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;
>
> c) amplifying the one or more oligonucleotide extension products, in the reaction mixture, using a first primer that

anneals to the complement of the first adaptor sequence and a second primer that anneals at its 3′ end to a complement of the second adaptor sequence, thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest; and

d) sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

Ex. 1002, 35:18–51.

E. Asserted Challenges to Patentability

Petitioner asserts the following challenges to patentability:

Claims Challenged	35 U.S.C. §[1]	Reference
1, 3, 5–10, 14–18	102	Meyer[2]
8, 17, 18	103(a)	Meyer
2	103(a)	Meyer, Siebert[3]

[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. AIA §§ 3(b), 3(c), and 3(n). The '108 patent claims priority to a provisional application filed on January 26, 2012. Ex. 1002, code (60). Petitioner's challenge assumes this earliest potential priority date (Pet. 26) and Patent Owner provides no argument to the contrary. Accordingly, we apply the pre-AIA version of §§ 102 and 103.

[2] Meyer et al., *Sequencing and* de novo *analysis of a coral larval transcriptome using 454 GSFlx*, 10:219 BMC GENOMICS (2009) (Ex. 1006, "Meyer").

[3] Siebert et al., *An improved PCR method for walking in uncloned genomic DNA*, 23(6) NUCLEIC ACIDS RESEARCH 1087–88 (1995) (Ex. 1007, "Siebert").

Claims Challenged	35 U.S.C. §[1]	Reference
11, 12, 19	103(a)	Meyer, Caruccio[4], Bronner[5]

In support of their respective positions, Petitioner relies on the Declaration of Peter A. Sims, Ph.D. (Ex. 1085), and Patent Owner relies on the Declaration of Carlos D. Bustamante, Ph.D. (Ex. 2021).

II. DISCRETIONARY DENIAL

Institution of an *inter partes* review is discretionary. *See Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 273 (2016) (explaining that because 35 U.S.C. § 314 includes no mandate to institute review, "the agency's decision to deny a petition is a matter committed to the Patent Office's discretion"); *see also Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (stating that under § 314(a), "the PTO is permitted, but never compelled, to institute an IPR proceeding").

Under 35 U.S.C. § 325(d), in determining whether to institute an *inter partes* review, "the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." Our § 325(d) analysis employs a two-prong framework: (1) whether the art or arguments presented in the petition are the same or substantially the same as those previously presented to the Office; and (2) if so, whether the petitioner has demonstrated a material error by the Office in its prior consideration of the

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[4] Caruccio, *Preparation of next-generation sequencing libraries using Nextera™ technology: simultaneous DNA fragmentation and adaptor tagging by in vitro transposition*, *in* HIGH-THROUGHPUT NEXT GENERATION SEQUENCING: METHODS AND APPLICATIONS, 733 METHODS IN MOLECULAR BIOLOGY Ch. 17 (2011) (Ex. 1008, "Caruccio").

[5] Bronner et al., *Improved Protocols for Illumina Sequencing*, 18 CURR. PROTOC. HUM. GENET. (2009) (Ex. 1009, "Bronner").

art or arguments. *Advanced Bionics, LLC v. Med-El Electromedizinishe Geräte GmbH*, IPR2019-01469, Paper 6, 8 (PTAB Feb. 13, 2020) (precedential).

Patent Owner argues that we should exercise our discretion to deny institution under § 325(d). Prelim. Resp. 38–43. According to Patent Owner, "the arguments raised by Petitioner are substantially the same as the arguments the Examiner considered," and "Petitioner fails to demonstrate a material error by the Office." *Id.* We are not persuaded by Patent Owner's arguments.

A. Relevant Prosecution History of the '108 Patent

The '108 patent issued from U.S. Patent Application No. 16/017,340 ("the '340 application"). Ex. 1002, code (21). During prosecution, the examiner rejected the then-pending claims as obvious over, among other references, U.S. Patent Publication No. 2005/0142577 ("Jones 2005"). Ex. 1017, 2420.

In response, the applicant submitted a declaration of Dr. Andrew Brooks. *Id.* at 2503–07. Dr. Brooks explained that "the claimed methods involve annealing and extending a target-specific primer to enrich a sequence of interest (rather than, for example, annealing a forward target-specific and reverse target-specific primer pair at a sequence of interest and performing a polymerase chain reaction with the forward target-specific and reverse target-specific primer)." *Id.* at 2505. He stated that he "was skeptical that the claimed methods would provide efficient sequencing data." *Id.* He further testified that he "observed unexpected results when enriched nucleic acid sequences generated using the claimed methods were sequenced by massively parallel sequencing." *Id.* at 2506; *see*

also id. ("Based on my knowledge and experience in this field, I did not expect and would not have predicted this level of specificity.").

The Examiner found Dr. Brooks' declaration sufficient to overcome the obviousness rejections and allowed the claims. *Id.* at 2565–66.

B. Analysis

Petitioner asserts that Meyer anticipates claims 1, 3, 5–10, and 14–18. Pet. 28–61. In other words, Petitioner argues that Meyer discloses each and every limitation of these claims.

Meyer was not before the Examiner during prosecution of the '340 application. *See generally* Ex. 1017. Patent Owner, however, contends that "[t]he Examiner issued rejections, arguing that Jones 2005 taught the same elements that Petitioner claims Meyer discloses." Prelim. Resp. 39 (citing 2420–25). We disagree.

During prosecution of the '340 application, the Examiner specifically acknowledged that Jones 2005 "does not teach massively parallel sequencing as required by" the claim that issued as independent claim 1. Ex. 1017, 2421. Thus, contrary to Patent Owner's assertion, the Examiner did not find Jones 2005 "discloses each limitation of claim 1 of the '108 patent." *See* Prelim. Resp. 39. In other words, the Examiner did not make "the same arguments with respect [to] Jones 2005 publication during the prosecution of the '340 application." *Id.* As a result, Petitioner's anticipation challenge based on Meyer is not the same or substantially the same as the Examiner's obviousness rejections based on Jones 2005.

Patent Owner also argues that the Examiner made the same arguments with respect to the Jones 2005 publication during the prosecution of the

parent and grandparent applications of the '340 application.[6] *Id.* As support, Patent Owner points to an office action issued during the prosecution of the '340 application's grandparent application. *Id.* (citing Ex. 2019, 6–13). There, the Examiner rejected the claims-at-issue as anticipated by Jones 2005.[7] Patent Owner does not show what limitations those claims recite. The record before us, however, shows the Examiner relied on Jones 2005 for disclosing "sequencing the enriched nucleic acid of interest," without discussing massively parallel sequencing, which is required by the challenged claim 1. *See* Ex. 2019, 9–10.

On this record, Patent Owner has not sufficiently supported its argument that "Jones 2005 taught the same elements that Petitioner claims Meyer discloses." *See* Prelim. Resp. 39. As a result, Petitioner's anticipation challenge based on Meyer is not the same or substantially the same as the Examiner's anticipation rejection based on Jones 2005.

C. Conclusion

Because the Petition does not present the same or substantially the same prior art or arguments previously considered by the Examiner, we decline to exercise our discretion to deny the Petition under § 325(d).

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[6] Patent Owner does not dispute that Meyer was not before the Examiner during prosecution of the '340 application's parent and grandparent applications either.

[7] In the same office action, the Examiner also rejected the claims-at-issue as anticipated by U.S. Patent Publication No. 2003/0232348 ("Jones 2003"). Ex. 2019, 6. Patent Owner, however, does not argue Jones 2003 or the Examiner's rejection based on Jones 2003 constitutes the same or substantially the same art or arguments under § 325(d). *See generally* Prelim. Resp. 38–40.

III. ANALYSIS

A. Level of Ordinary Skill in the Art

In determining the level of ordinary skill in the art, various factors may be considered, including the "type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field." *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Furthermore, the prior art itself can reflect the appropriate level of ordinary skill in the art. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Petitioner asserts that:

> Because the '108 patent is directed to library preparation and data interpretation methods for NGS, the POSA [person of ordinary skill in the art] could have had academic training in any of a variety of fields that used NGS, including chemistry, molecular biology, biochemistry, or medicine. The POSA would have a PhD or equivalent training in one of those fields and several years of work experience (or commensurately less education and more work experience). The POSA further would have had specific experience with implementing and designing library preparation methods for 454 and Illumina, the leading NGS platforms in 2012. This would have included specific experience with, and understanding of, the sequences contained in adaptors for 454 and Illumina sequencing at the priority date, and the chemistry used to attach those adaptors to DNA fragments prior to sequencing.

Pet. 23–24 (citing Ex. 1085 ¶¶ 121–23).

Patent Owner disagrees with Petitioner's proposed definition. Prelim. Resp. 14–16. Patent Owner contends that "[t]he sequencing methods described in the '108 patent do not require a Ph.D. to understand and perform." *Id.* at 15. According to Patent Owner, the level of education for a POSA "is more appropriately a Ph.D. in a field related to molecular biology,

or a B.S. or M.S. degree with three to five years of experience working in a molecular biology lab." *Id.* at 15 (citing Ex. 2021 ¶¶ 65–68).

We do not see a material difference in the parties' proposed levels of education and work experience. Indeed, although Petitioner asserts that a POSA "would have a PhD or equivalent training," it allows more work experience to compensate for less education. Pet. 23 (stating that a POSA could have "commensurately less education and more work experience"). We, nevertheless, adopt Patent Owner's proposal in this aspect because it specifies the years of experience needed.

Patent Owner also disputes Petitioner's proposal that a POSA would have had experience with "implementing and designing library preparation methods 454 and Illumina, the leading NGS platforms in 2012." *Id.* at 15 (quoting Pet. 23, emphasis added by Patent Owner removed). According to Patent Owner, "[t]his level of skill inappropriately requires the POSA to be an *inventor* of library preparation methods." *Id.* On this record, we agree with Patent Owner that "experience with implementing and designing library preparation methods 454 and Illumina" is above ordinary skill.

We, however, find insufficient Patent Owner's proposal that "the POSA would have had experience with DNA sequencing methods." *Id.* at 15–16 (citing Ex. 2021 ¶¶ 65–68). The challenged claims relate to sequencing methods using a next-generation sequencing ("NGS") platform. *See* Ex. 1002, 35:49–51 (claim 1 reciting "sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform"). As Patent Owner recognizes,

> [c]ompared to traditional, Pre-NGS sequencing methods, NGS sequencing utilized a new design that no longer relied upon disassembling and then piecing together a single original template DNA strand. Instead, NGS sequencing now allowed

> for hundreds of thousands of original template strands to be sequenced in the same reaction. With NGS, a user could perform massively parallel sequencing, allowing for elements of the genome to be sequenced in a fast, scalable manner.

Prelim. Resp. 4. As such, we disagree with Patent Owner that a POSA only need to "have had experience with DNA sequencing methods" (*id.* at 15–16) because an artisan with experience with only pre-NGS sequencing methods would not qualify as a POSA.

Instead, for purposes of this Decision, we find a POSA would have had a Ph.D. in the field of chemistry, molecular biology, or biochemistry. Alternatively, a POSA would have had a B.S. or M.S. degree with three to five years of experience working in any of those fields. Additionally, the POSA would have had experience with NGS sequencing methods and a working knowledge of how those methods functioned. This definition of a POSA is consistent with the skill level reflected in the disclosures of the '108 patent and prior art. We further note that neither aspect of the dispute over the skill level affects our decision to institute review.

B. Claim Construction

In an *inter partes* review, we construe a claim term "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b)." 37 C.F.R. § 42.100(b) (2020). Under that standard, the words of a claim "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Petitioner proposes that we construe the terms "sequence of interest" and "barcode." Pet. 24–25. According to Petitioner, the '108 patent defines

"sequence of interest," which is used interchangeably with terms "target nucleic acid sequence" and "target sequence," as "a polynucleotide sequence of interest, for which enrichment is desired." *Id.* at 24 (citing Ex. 1002, 21:3–5, 21:8–11). Patent Owner does not dispute Petitioner's proposed construction of this term.[8] *See* Prelim. Resp. 17. On this record, we adopt Petitioner's proposed construction of the term "sequence of interest."

Petitioner also proposes that we construe the term "barcode." Pet. 25. Patent Owner points out that the term "barcode" only appears in dependent claim 8 and argues that we do not need to construe this term. Prelim. Resp. 17. For purposes of this Decision, we agree with Patent Owner on this issue.

Neither party proposes any special meaning for the term "enrich." We see no reason to do so either. To the extent express construction of "enrich" is necessary, we adopt the plain and ordinary meaning of the term. *See* Ex. 3001 (entry e defining "enrich" to mean "to process so as to add or increase the proportion of a desirable ingredient").

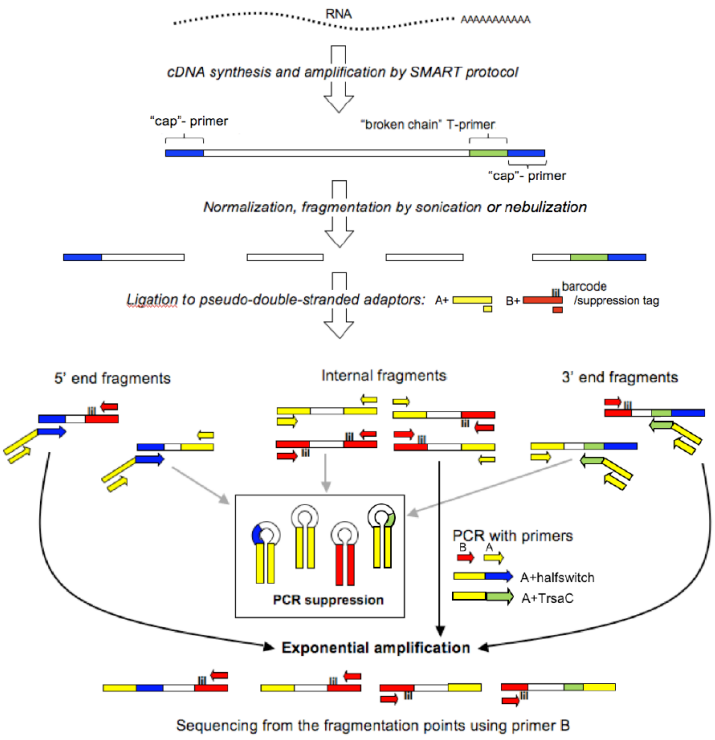
Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to construe any other claim term expressly.

[8] Patent Owner, however, states that it "does not agree with Petitioner's application of the 'for which enrichment is desired' portion of the proposed construction." *See* Prelim. Resp. 17. We address the *application* of claim construction below when discussing the patentability of the challenged claims.

C. Disclosure of Meyer

Meyer describes improved methods for cDNA library preparation and titration for *de novo* transcriptome sequencing of organisms using 454 sequencing, as well as strategies for assembling a useful catalog of genes from the output. Ex. 1006, Abstract, 2.

Meyer describes a method for sequencing and analysis of coral larval cDNA. *Id.* at 2, 12–17, Fig. 1. In Additional File 4,[9] Meyer also describes a second method that includes minor modifications to improve reproducibility and further reduce the occurrence of adaptor concatenation. *Id.* at 14, 19–25. Meyer's second method is schematically illustrated in the figure reproduced below.



[9] Additional File 4 is part of a set of additional files appended to Meyer and includes a step-by-step protocol for a library preparation method. *See* Ex. 1006, 14.

The figure above is a color schematic showing an improved protocol for transcriptome analysis in emerging model organisms, as described in Meyer's Additional File 4. *Id.* at 20.

In the first step of this method, cDNA is synthesized and amplified from RNA using the SMART™ PCR cDNA Synthesis Kit from Clontech and a synthesis primer with a "cap" primer sequence at the 5′ end and a "broken chain" polyT at the 3′ end. *Id.* at 19–20. The "broken chain" polyT primer is used "to reduce read artifacts during 454 pyrosequencing, which may get thrown out of calibration by too strong of a light signal produced from a long mononucleotide stretch (such as polyT or polyA)." *Id.*

In the second step, the cDNA may be normalized and reamplified using the "cap" primer, and is fragmented to an average size of 350–400 bp using sonication or nebulization. *Id.* at 19–20.

Third, the cDNA fragments are end-polished by incubation with a DNA polymerase and dNTPs, and then ligated to pseudo-double-stranded A+ and B+ adaptors at the "new" 5′ ends. *Id.* at 19; *see also id.* at 20. The A+ and B+ adaptors each contain an equimolar mixture of: (1) a long oligo that gets ligated at its 3′ end and contains the standard 454 A or B primer sequence, respectively; and (2) a short oligo that is complementary to the 3′ end of the long oligo to mimic the double-stranded blunt end for the ligase enzyme. *Id.* at 19. According to Meyer, "[t]he short oligo is not ligated since it lacks a 5′-phosphate." *Id.*

In the fourth step, the library is amplified using a mixture of the standard 454 A and B primers and two long "step-out" primers: A+TRSAC and A+halfswitch. *Id.* at 19–20. Meyer explains that "suppression tags" are used to "invoke a PCR suppression effect for the fragments that end up

flanked by the same kind of adapter, which results in exclusive amplification of the fragments flanked by both A and B primers." *Id.*

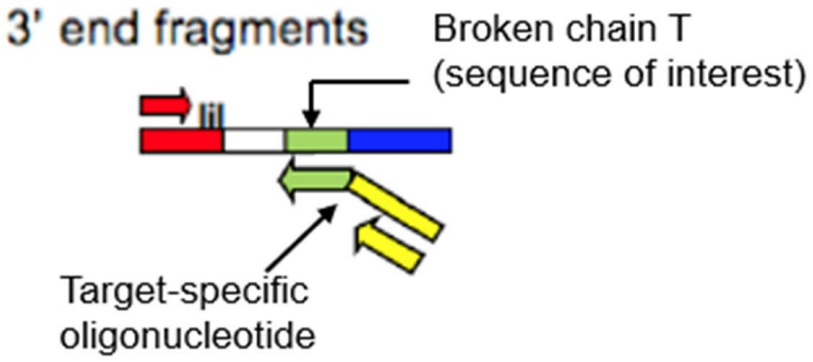
In the final step, the fragments are sequenced from their fragmentation points using the B primer. *Id.* at 20.

D. Alleged Anticipation by Meyer

Petitioner asserts that Meyer anticipates claims 1, 3, 5–10, and 14–18. Pet. 28–60. Based on this record, and for at least the following reasons, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion.

We focus our analysis on independent claim 1. Claim 1 is directed to a method for sequencing an enriched nucleic acid sequence of interest. Ex. 1002, 35:18–19. In particular, step (a) recites "the nucleic acid fragment ligated to a partial duplex adaptor, wherein the nucleic acid fragment comprising the nucleic acid sequence of interest." *Id.* at 35:24–25. In addition, step (c) recites "amplifying the one or more oligonucleotide extension products . . . thereby enriching the nucleic acid sequence of interest." *Id.* at 35:41–46.

Petitioner provides detailed analysis to support its argument that Meyer discloses each limitation of claim 1. Pet. 42–50. Specifically, Petitioner draws our attention to the following figure.



The figure above is Petitioner's annotation of a portion of the schematic illustration of the protocol described in Meyer's Additional File 4. *Id.* at 44. Petitioner argues that the broken chain T primer sequence (green box) is the claimed "nucleic acid sequence of interest." *Id.* at 45. According to Petitioner, "the broken chain T primer sequence was specifically targeted by a 'target-specific oligonucleotide' (green and yellow)." *Id.* Petitioner maps the red adaptor as the claimed "first adaptor" and the yellow adaptor as the claimed "second adaptor. *Id.* at 45–47. Petitioner also argues that the claimed "nucleic acid fragment" is "the 3′ end adaptor-ligated fragments," which includes "a first adaptor sequence, the red adaptor, the white unknown fragment sequence, the green broken chain T sequence that the green-yellow primer annealed to, and the blue cap primer sequence." *Id.* at 44–46 (citing Ex. 1006, 19–20; Ex. 1085 ¶¶ 133, 190–196, 268–270).

Petitioner contends that, in Meyer, after ligation of the red adaptor, a green and yellow "fragment-specific oligonucleotide" was annealed to the green nucleic acid sequence of interest. *Id.* at 44 (citing Ex. 1006, 20; Ex. 1085 ¶¶ 133, 190–196, 268–270). Petitioner contends that extending the green-yellow primer in Meyer's anchored PCR reaction resulted in an extension product "comprised of a sequence complementary to the red adaptor sequence at one end, the complement of the target fragment in the middle, and the green-yellow primer sequence, including the yellow adaptor, on the other end." *Id.* at 47 (citing Ex. 1006, 20; Ex. 1085 ¶ 198, 271, 272).

According to Petitioner, subsequent PCR reactions amplified the extension product using primers complementary to the red and yellow adaptors and generated "a library of double-stranded DNA products containing the 'sequence of interest' (green broken chain T primer) and the adjacent mRNA fragment sequence, sequence, flanked by the 'first adaptor

sequence' (containing the red 'B' adaptor) at one end, and the 'second adaptor sequence' (yellow 'A' adaptor) at the other end." *Id.* at 48–51 (citing Ex. 1006, 20; Ex. 1085 ¶¶ 199, 200, 273, 274). Petitioner asserts that "these fragments were found at a greater prevalence than fragments at other portions of the strand, thus confirming that they were enriched compared to other mRNA fragments." *Id.* at 50; *see also id.* at 40 ("The result of that amplification was to enrich for the 3′ end fragments compared to other cDNA fragments present in the sample that lacked the requisite adaptors.") (citing Ex. 1006, 20; Ex. 1085 ¶¶ 143, 144, 266, 267, 168–175, 182).

Patent Owner disagrees. Prelim. Resp. 17–35. According to Patent Owner, Meyer discloses a method for sequencing an entire coral transcriptome, and "[t]here is no polynucleotide sequence disclosed in Meyer that is specifically targeted for enrichment and sequencing over other sequences in the sample." *Id.* at 18, 31 (citing Ex. 1006, 12; Ex. 2021 ¶¶ 108–123). As a result, Patent Owner contends that Meyer does not disclose a "sequence of interest." *Id.* at 31–34. Patent Owner also argues that Meyer does not disclose "amplifying . . . to enrich" because Meyer's method is directed to reducing sequencing read artifacts. *Id.* at 24–31.

On this record, we find Petitioner's arguments more persuasive than Patent Owner's arguments, which we address below.

1. Enrichment

Meyer discloses a method for sequencing the coral transcriptome. Ex. 1006, 1. It is undisputed that the polyA tails at the 3' ends of intact transcripts "can be hundreds of nucleotides long." Ex. 1085 ¶ 148. Meyer explains that "454 sequencing does not efficiently process homopolymer regions greater than 8 bp in length," and thus, the long polyA tails "would be expected to result in under-representation of the 3' ends of transcripts."

Ex. 1006, 9. Meyer discloses that a broken T adaptor or broken chain T-primer, i.e., "simply interrupting the poly-T region with a single C," resolves this issue. *Id.*

Patent Owner asserts that Meyer does not disclose enrichment because it "never discloses increasing the percentage of the sequence of interest as compared to any other component of the sample." Prelim. Resp. 25. But contrary to this assertion, Meyer specifically discloses that a single copy of the broken chain T-primer was found in "16% of the total" raw reads, "slightly more than the expectation (~10%)." Ex. 1006, 9.

If the expected 3' end fragments are 10% of the total reads, the combined 5' end fragments and internal fragments would be 90%. By employing the broken chain T-primer, Meyer increased the percentage of the 3' end fragments to 16% of the total reads, which means the combined 5' end fragments and internal fragments would be decreased to 84%. In other words, Meyer discloses increasing the percentage of the 3' end fragments, which contains the broken chain T-primer sequence, as compared to the 5' end fragments and internal fragments. Patent Owner does not explain persuasively why, under such circumstances, enrichment is not met.

Patent Owner emphasizes that Meyer "is directed toward improving the error rate of sequencing reads." Prelim. Resp. 26 (citing Ex. 2021 ¶¶ 124–130); *see also id.* at 28 ("The 'homopolymer problem' that Meyer was trying to fix is an issue caused by the 454 sequencer."). We agree with Patent Owner on this issue. Patent Owner, however, has not explained sufficiently why Meyer's method of reducing read artifacts by increasing the proportion of 3' end fragments in the total read does not meet the claimed enrichment.

Patent Owner argues that even accepting Petitioner's interpretation of "enrich," Petitioner's challenge still would fail because the raw read data Petitioner relies on "did not concern the modified method disclosed in additional file 4." Prelim. Resp. 29 (citing Ex. 2021 ¶¶ 128–135); *see also id.* at 28 ("Petitioner does not point to any data regarding alleged 'enrichment' seen in the modified method."). Instead, Patent Owner contends that "Meyer reports raw reads from using the method disclosed in Figure 1 of the publication, which used primers specific to the cap primers at both the 5′ and 3′ end fragments." *Id.* at 29 (citing Ex. 1006, 2–3; Ex. 2021 ¶ 113).

Patent Owner is correct that the data reported in Meyer were generated using the method of Figure 1, whereas Petitioner relies on the method in Additional File 4 for its challenge. *See* Ex. 1006, 12; Pet. 29. To the extent Patent Owner argues that the Petition must point to actual data from method in Additional File 4 to show enrichment, we disagree. "Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003). Here, Meyer, a prior art printed publication, enjoys the presumption of enablement. *In Re Antor Media Corp.*, 689 F.3d 1282, 1289 (Fed. Cir. 2012).

Moreover, Meyer touts the method in Additional File 4 as an improvement over the one in Figure 1. Ex. 1006, 14, 19. Patent Owner does not argue, and we find no evidence to suggest, that this improved method would generate fewer reads of the 3′ end fragments than the 16% reported in Meyer. Thus, the lack of enrichment data from Meyer's method in Additional File 4 is not fatal to Petitioner's challenge.

Patent Owner further points out that Meyer's expectation of 10% of the total reads are 3′ end fragments is based on average read length of 232 bp and assuming an average transcript size of 2,200 bp. Prelim. Resp. 30 (citing Ex. 1006, 9). Citing the testimony of its declarant, Patent Owner argues that "Meyer's estimate is very likely flawed." *Id.* According to Patent Owner, "the distribution data reported by Meyer show[] that the transcript lengths skewed heavily towards being far less than" the assumed 2,200 bp. *Id.* at 31 (citing Ex. 2021 ¶¶ 131–134). "Had Meyer instead assumed that the average length of the transcripts was 1,450 bp (which is not unreasonable given the reported distribution)," Patent Owner concludes, "Meyer's expectation would have been 16%." *Id.*

Patent Owner's challenge of Meyer's assumption of the average transcript size involves fact intensive issues better resolved after the parties fully develop the record during trial. Additionally, Meyer reports that, in its method, 16% of the total reads are 3′ end fragments, "slightly more than the expectation." Ex. 1006, 9. Patent Owner appears to emphasize the word "slightly" in Meyer's disclosure. Prelim. Resp. 31. Patent Owner, however, has not proposed to construe the term "enrich" to require a minimum increase. Thus, at this preliminary stage, we find Meyer's method increases the proportion of the 3′ end fragments from the expected 10% to the reported 16%, sufficient to meet the term "enrich."

On this record and for purposes of institution, we find Petitioner has shown sufficiently that Meyer discloses enrichment of the 3′ end fragments, which include the broken chain T primer sequence.

2. Nucleic Acid Sequence of Interest

Patent Owner argues that Meyer does not disclose enrichment of a "nucleic acid sequence of interest." Prelim. Resp. 31–34. According to

Patent Owner, the broken chain T primer is not the "sequence of interest" because it is "simply a tool for promoting sequence read fidelity" and its enrichment is not "desired." *Id.* at 32 (citing Ex. 2021 ¶¶ 124–130, 136–141). Patent Owner's argument is unavailing.

Indeed, as Petitioner argues, Meyer employed the broken chain T-primer to ensure that sequences near the 3′ end of mRNA molecules were adequately represented in the final sequencing data. Pet. 30 (citing Ex. 1006, 9; Ex. 1085 ¶ 143). Patent Owner does not dispute this argument. *See* Prelim. Resp. 19, 24 (citing Ex. 1006, 9; Ex. 2021 ¶ 85). Instead, Patent Owner emphasizes that Meyer is interested in, not the broken chain T-primer, but the "sequence information from ***near*** the polyA of the mRNA." *Id.* at 33 (quoting Pet. 42, emphasis added by Patent Owner).

To obtain sequence information from near the 3′ end of the mRNA, however, the 3′ end fragments need to be sufficiently represented. Meyer explains that its method generated more than expected raw reads containing the broken chain T-primer, which "suggests that the 3' ends of transcripts were well-represented in [the] dataset, confirming the effectiveness of this solution for overcoming the homopolymer problem." Ex. 1006, 9. This statement indicates that the enrichment of the broken chain T-primer is in fact desired.

On this record and for purposes of institution, we find Petitioner has shown sufficiently that the broken chain T primer sequence in Meyer is a sequence of interest.

3. Summary

Based on the current record and for purposes of institution, we find Petitioner has shown sufficiently that Meyer discloses the limitations of claim 1, arranged as claimed. In other words, Petitioner has established a

reasonable likelihood of prevailing on its assertion that Meyer anticipates claim 1. We, thus, institute trial to review the challenged claims of the '108 patent.

Petitioner also asserts that Meyer anticipates claims 3, 5–10, and 14–18. Pet. 50–60. Patent Owner does not argue these claims separately. *See* Prelim. Resp. 35. In any event, we institute an *inter partes* review as to all challenges raised in the Petition. *See SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348, 1356 (2018); *see also* 37 C.F.R. § 42.108(a) ("When instituting *inter partes* review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim.").

E. Other Challenges

Petitioner asserts that (1) claims 8, 17, and 18 would have been obvious over Meyer (Pet. 61–62); (2) claim 2 would have been obvious over the combination of Meyer and Siebert (*id.* at 62–65); and (3) claims 11, 12, and 19 would have been obvious over the combination of Meyer, Caruccio, and Bronner (*id.* at 66–69).

Patent Owner disagrees. Prelim. Resp. 36–38. According to Patent Owner, the Petition does not identify which elements of Meyer would be modified to arrive at claim 1, does not explain why a POSA would have been motivated to make those modifications, and does not address whether the POSA would have had a reasonable expectation of success in making such modification. *Id.* at 36. Thus, Patent Owner argues that the Petition fails to show claim 1 is obvious over Meyer. *Id.* at 37. Patent Owner also asserts that all the obviousness challenges fail for the same reasons that Meyer fails to anticipate or render obvious claim 1. *Id.* at 37–38.

As discussed above, we determine that Petitioner has shown a reasonable likelihood of proving that Meyer anticipates claim 1. *See supra* Section III.D. As a result, institution of an *inter partes* review is warranted as to all challenged claims on all grounds asserted in the Petition. *See SAS*, 138 S. Ct. at 1356. The parties will have opportunities to address the additional challenges after institution.

IV. CONCLUSION

Based on the current record, and for the reasons explained above, we find Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. We, therefore, institute an *inter partes* review of all challenged claims on all asserted grounds.

This Decision is not a final determination on the patentability of any challenged claim. Our view with regard to any conclusion reached in the foregoing could change upon further development of the record during trial. We remind the parties that any argument not raised in a Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed forfeited and/or waived even if asserted in the Preliminary Response. *In re Google Tech. Holdings LLC*, 980 F.3d 858, 862–864 (Fed. Cir. 2020) (holding an argument forfeited when not timely raised before the Board); *In re NuVasive, Inc.*, 842 F.3d 1376, 1380–81 (Fed. Cir. 2016) (holding Patent Owner waived an argument addressed in the Preliminary Response by not raising the same argument in the Patent Owner Response).

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), *inter partes* review is hereby instituted on all challenged claims of the '108 patent based on the asserted grounds set forth in the Petition; and

FURTHER ORDERED, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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