

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC,
Petitioner,

v.

BRUKER SPATIAL BIOLOGY, INC.,
Patent Owner.

Case IPR2023-01300
U.S. Patent No. 11,473,142

**PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY FOR
INTER PARTES REVIEW OF U.S. PATENT NO. 11,473,142**

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EXHIBIT LIST

Exhibit No.	Description
EX2001	USER Enzyme, https://www.neb.com/en-us/products/m5505-user-enzyme
EX2002	MEGAscript T7 Transcription Kit, https://www.thermofisher.com/order/catalog/product/AM1333
EX2003	Nanostring Technologies, Inc.’s Notice of Motion and Motion for an Order Confirming, Restating and Enforcing the Protections of Section 362 of the Bankruptcy Code with Respect to <i>Inter Partes</i> Review Proceedings Before the Patent Trial and Appeal Board, <i>In re: Nanostring Technologies, Inc., et al.</i> , Case No. 24-10160 (Bankr. D. Del.), March 4, 2024
EX2004	Order Confirming, Restating and Enforcing the Protections of Section 362 of the Bankruptcy Code with Respect to <i>Inter Partes</i> Review Proceedings, <i>In re: Nanostring Technologies, Inc., et al.</i> , Case No. 24-10160 (Bankr. D. Del.), March 4, 2024
EX2005	Declaration of Edward R. Reines in Support of Motion for <i>Pro Hac Vice</i> Admission, dated July 19, 2024
EX2006	<i>In re Edward R. Reines</i> , Case No. 14-MA004, Doc. 16 (Fed. Cir. 2014)
EX2007	Li, Y., et al., “Advances in ligase-based nucleic acid amplification technology for detecting gene mutations: a review,” <i>Molecular and Cellular Biochemistry</i> , Vol. 478, pp. 1621-1631 (2023)
EX2008	Declaration of Dr. David H. Sherman, Ph.D., in Support of Patent Owner’s Response
EX2009	Transcript from the deposition of Paul T. Spellman, Ph.D., taken on Nov. 7, 2024
EX2010	Ali, M., et al., “Rolling circle amplification: a versatile tool for chemical biology, materials science and medicine,” <i>Chem. Soc. Rev.</i> , Vol. 43, pp. 3324-3341 (2014)
EX2011	Mills, J., et al., “Strand-Specific RNA-Seq Provides Greater Resolution of Transcriptome Profiling,” <i>Current Genomics</i> , Vol. 14, No. 3, pp. 173-181 (2013)

EX2012	Zhao, S., et al., "Comparison of stranded and non-stranded RNA-seq transcriptome profiling and investigation of gene overlap," BMC Genomics, Vol. 16, No. 675 (2015)
EX2013	Mercier, J., et al., "Solid Phase DNA Amplification: A Brownian Dynamics Study of Crowding Effects," Biophysical Journal, Vol. 89, No. 1, pp. 32-42 (2005)
EX2014	Roy, S., et al., "Synthesis of DNA/RNA and Their Analogs via Phosphoramidite and H-Phosphonate Chemistries," Molecules, Vol. 18, pp. 14268-14284 (2013)
EX2015	Kalle, E., et al., "Multi-template polymerase chain reaction," Biomolecular Detection and Quantification, Vol. 2, pp. 11-29 (2014)
EX2016	MEGAscript Kit User Guide, Ambion by Life Technologies, Publication No. 1330M, Revision G (Sept. 14, 2012)
EX2017	Curriculum Vitae of Dr. David H. Sherman, Ph.D.
EX2018	Transcript from the deposition of Paul T. Spellman, Ph.D., taken on Mar. 18, 2025

I. INTRODUCTION

In its Reply, Petitioner confirms that it identified solely the first-strand cDNA in Stahl and So-456 as the claimed “DNA products.” As Patent Owner (“PO”) previously established, however, these first-strand cDNA products are not sequenced and do not incorporate location-identifying sequences during their synthesis; hence, they cannot satisfy the claims. Petitioner presents nothing in its reply to remedy this defect in its original Petition.

Rather than attempting to establish that the prior art maps to the claims, Petitioner spends most of its energy trying to map the prior art to Petitioner’s district court infringement contentions. This, however, is the wrong analysis altogether. For invalidity, the prior art must map to the *claims*, not Petitioner’s results-oriented interpretation of PO’s contentions from another proceeding. The folly of this approach is on full display here because Petitioner undeniably interprets PO’s contentions erroneously. Indeed, while Petitioner’s invalidity theory is based on accusing the first-strand cDNA products in Stahl and So-456, PO’s infringement contentions identify Visium FF’s *second-strand* cDNA as the claimed “DNA products” synthesized via a two-step process, as explained by PO and understood by the Board. Petitioner’s theory thus misses the boat completely, and its attempt to double down on a theory that relies upon a misguided interpretation of PO’s

infringement contentions simply cements its failure to set out a *prima facie* case of invalidity.

To the extent Petitioner now seeks to alter its original infringement theory and rely upon new aspects of Stahl and So-456 as constituting the claimed “DNA products,” it presents at most a half-hearted argument that is inadequately developed. And, in any event, any attempt by Petitioner to now alter its original theory is improper and should not be permitted. *See Consolidated Trial Practice Guide* (Nov. 2019) at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a *prima facie* case of unpatentability.”).

For these reasons, and the additional reasons stated herein, the Petition should be rejected.

II. STAHL DOES NOT ANTICIPATE CLAIMS 1-13

A. Stahl Does Not Disclose Sequencing The Claimed DNA Products

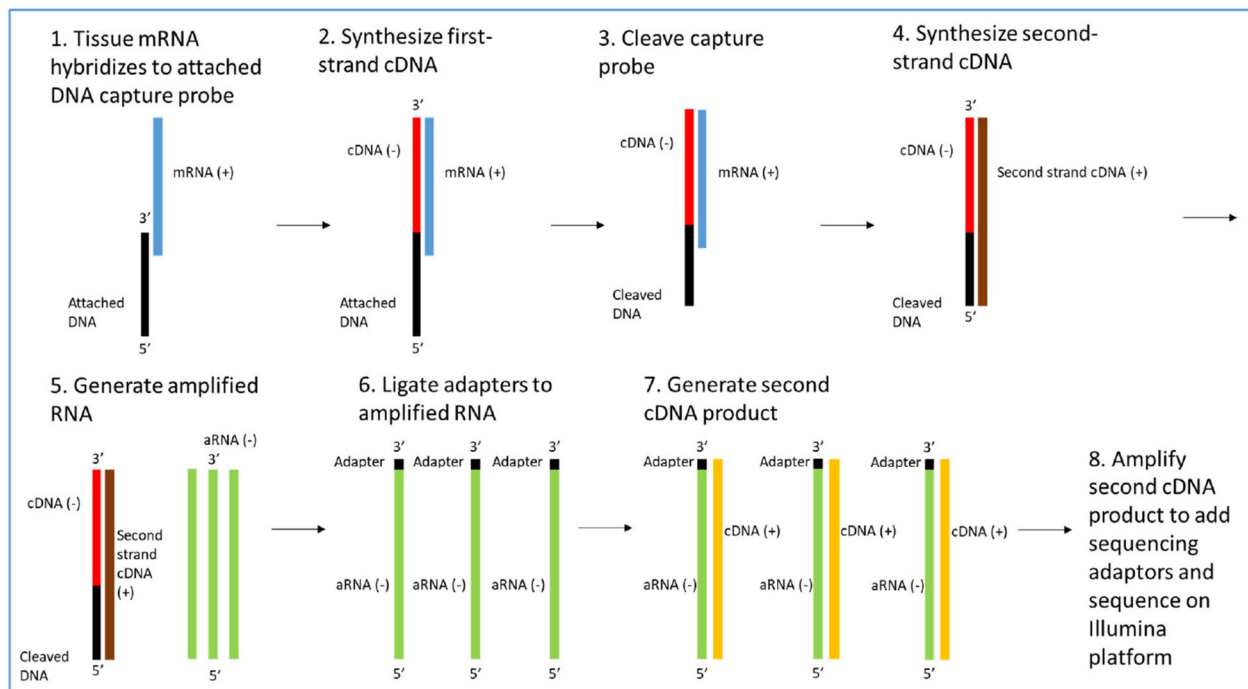
Petitioner does not deny that claim 1(e) requires sequencing “DNA products” that were “synthesized” in steps 1(c) and 1(d). As PO explained, the Petition identified solely the first-strand cDNA in Stahl as the synthesized “DNA products,” and the first-strand cDNA in Stahl is *not* sequenced. *See Paper 31* (“PO’s Response”) at 23-31. Petitioner’s expert confirmed this at cross-examination:

Q: Is it your opinion that in your first declaration you identified the first-strand cDNAs in Stahl, the entire strand including the capture probe and the synthesized cDNA as the DNA products of claim 1's steps (c) and (d)?

A: Under the initial infringement position and my understanding of the -- of the terms at the time, I believe that that is correct.

EX2018 at 57:3-11.

Petitioner does not deny that Stahl sequences a second cDNA product and **not** the first-strand cDNA, as is clear from Dr. Sherman's depiction of Stahl's method:



Paper 31 ("PO's Response") at 29; EX2008 ¶ 46. The first-strand cDNA synthesized in step 2 (shown in red) is not the second cDNA product synthesized in

step 7 (shown in orange)—they are different molecules with different sequences. Thus, Stahl’s first-strand cDNA is not sequenced as required by the claims and Petitioner’s continued identification of the first-strand cDNA shows only that Petitioner has failed to meet its burden of proving the claims’ unpatentability.

Petitioner responds with three meritless arguments.

1. The First-Strand cDNA Does Not Satisfy PO’s Claim Interpretation

First, Petitioner contends that its identified “DNA products” meet “Bruker’s litigation interpretation, [where] claim 1(e) encompasses sequencing molecules that are not the first- or second-strand cDNA molecules per se, because the sequenced molecules also contain adapter and index sequences.” Paper 35 (“Response”) at 6-7. As support, Petitioner cites PO’s initial infringement contentions in parallel litigation, where the “Library Construction” and “Sequencing” steps of Petitioner’s Visium FF product are cited in a claim chart. *Id.*

Yet, Petitioner misrepresents PO’s litigation position when it posits that these contentions establish that *any* molecule generated downstream from the “DNA products” satisfies claim 1(e). The cited portions of PO’s infringement contentions that refer to adding adapters and index sequences do not suggest that these molecules with adapters and indices can be the claimed “DNA products.” In fact, the process of adding sequencing adapters and index sequences is part and parcel of Illumina

sequencing because these sequences are essential steps for sequencing on an Illumina platform. Consistent with this understanding that adding sequencing adapters and index sequences is part of sequencing, the patent specification explains that “the invention provides *a method of nucleic acid sequencing comprising* amplifying a library of nucleic acid templates...and carrying out a nucleic acid sequencing reaction....” EX1043 at 43:45-55.¹ PO’s initial infringement contentions identify *both* the steps of library construction—wherein sequencing adapters are added to the “DNA products”—and sequencing of the library on an Illumina sequencer as infringing claim 1’s step (e). They do not suggest that the DNA molecules with the adapters and indices are the claimed “DNA products.”

Thus, Petitioner’s assertion that PO’s infringement contentions support sequencing “DNA products” that are different from those synthesized in an earlier step is contrary to both the infringement contentions and the ’142 patent. In contrast, Petitioner’s identified first-strand cDNA in Stahl is transformed into a different molecule prior to sequencing, which includes the addition of sequences not essential to sequencing, due to the multiple intervening steps between first-strand cDNA synthesis and sequencing. See PO’s Response at 29-31.

¹ Emphasis added throughout unless noted.

Ultimately, whether Petitioner's invalidity mapping can be squeezed into some interpretation of PO's district court infringement theory is not the relevant inquiry here. Rather, Petitioner must meet its burden by identifying specific portions of Stahl and showing that the identified portions meet every claim element. This is so because the "IPR petition [] must provide an understandable explanation of the element-by-element specifics of the patentability challenges, including the identification of particular portions of prior art on which the petitioner is relying." *Corephotonics, Ltd. v. Apple Inc.*, 84 F.4th 990, 1001 (Fed. Cir. 2023).

Here, Petitioner identified Stahl's first-strand cDNA, a product that is far removed from the actual sequencing step. As shown in Dr. Sherman's diagram, numerous steps take place prior to sequencing, such as an *in vitro* transcription to generate amplified RNA, addition of a ligation adapter, and a second reverse transcription to generate the second cDNA product. See PO's Response at 29. Not only is the sequenced second cDNA product a different molecule from the first-strand cDNA, their sequences are also dissimilar, such as being inversely complementary and including the sequence of a ligation adapter. See PO's Response at 30-31. As Petitioner's expert explains, Stahl's second-strand cDNA and subsequent products also have sequences different from the first-strand cDNA

due to the use of random hexamers as primers during second-strand cDNA synthesis.
EX2018 at 41:22-43:1.

Petitioner also contends that PO's "portrayal of Stahl's 'deliberate effort' to perform 'stranded RNA sequencing' is a strawman argument because Stahl's sequencing library included molecules comprising the sequence of the captured mRNAs (sense (+) strand) *and* molecules comprising the complementary sequence (antisense (-) strand)." Reply at 7 (emphasis in original).

Stranded RNA sequencing, however, is about keeping track of the orientation of the nucleic acid strands, as shown in Stahl's method. *See* PO's Response at 8, 31. As Dr. Spellman explains, when the second cDNA product is amplified, a sequencing adapter (InPE1.0) is added to one end of the molecule and another sequencing adapter and index sequence (InPE2.0 and Index Primer) are added to the other end of the molecule. EX2018 at 48:13-51:15. Illumina paired-end sequencing further involves sequencing one strand during a first read and a complementary strand during a second read, with the order of the reads determined by the different adapters on each end of the molecule intended for sequencing. *Id.* at 9:13-13:7. In Stahl, the two reads of a paired-end sequencing run correspond to sequences from each end of the molecule, with one read for the location-identifying sequence and the other read for the unique sequence identifying the captured mRNA.

Id. at 18:15-20:15, 54:9-20. Accordingly, Stahl’s method deliberately keeps track of strand orientation. As Dr. Sherman explained, Stahl performs stranded RNA sequencing:

Well, if they want to preserve the strandedness, they have to get the sequence of the positive strand only. Right? That’s what they’re interested in. So whatever they’re doing, they’re preserving that strand sequence so they can match it with the messenger RNA.

EX1056 at 64:3-8; *see also id.* at 85:6-86:6.

2. Petitioner’s Invalidity Theory Is Inconsistent With The Board’s Claim Interpretation

Second, Petitioner contends that “Stahl teaches the claimed sequencing step” because “both the Board’s and Bruker’s IPR constructions encompass sequencing molecules that are different from the first-strand (and second-strand) cDNAs due to, e.g., addition of adapters and index sequences.” Reply at 10. This is little more than a repeat of the argument addressed immediately above in Part II.A.1.

Petitioner’s reliance on the Board’s and PO’s construction of “identifying a first plurality [and second plurality] of DNA products by sequencing” is without

merit.² Petitioner contends that under these constructions, “Stahl teaches sequencing a library of molecules generated from the amplified copies of the second-strand cDNAs.” Reply at 10-11. As Dr. Sherman’s diagram shows, however, the sequencing library is generated from the second cDNA product and *not* the second-strand cDNAs. See PO’s Response at 29; EX2008 ¶ 46.

In addition, the claim language is clear—“DNA products” are synthesized and then the “DNA products” are sequenced. The Board’s preliminary construction and both of PO’s proffered constructions do not eliminate that requirement. Petitioner’s identified first-strand cDNA, and even Stahl’s second-strand cDNA, are not sequenced, where sequencing, consistent with PO’s infringement position and the ’142 patent, includes amplification to add sequencing adapters and index sequences.

² Despite stating that the location-identifying nucleic acid sequences in the Board’s construction “are of course determined *by sequencing*,” Reply at 10 (emphasis in original), Petitioner provides no substantive disagreement with either of PO’s proffered constructions.

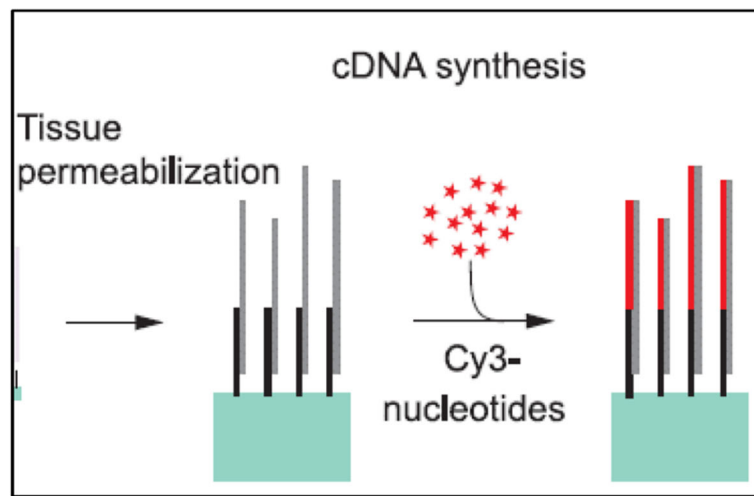
3. Petitioner Fails To Identify The Sequenced Strand

Third, Petitioner contends that it identified the first-strand cDNA with fluorescent nucleotides “in Stahl’s Figure 1A as *representative depictions of cDNA synthesis*, not as the claimed DNA products.” Response at 9 (emphasis in original).

Yet, Petitioner does not deny that it identified cDNA with Cy3-nucleotides in the Petition and that these synthesized cDNA are used for visualization, not sequencing. The section of the Petition corresponding to the synthesized “DNA products” is reproduced in full:

2. “c) [and (d)] synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction...”

Stahl discloses the synthesis steps (c) and (d) because Stahl’s method uses a reverse transcription reaction to “synthesize” cDNA products using the captured mRNAs as templates. EX1044, ¶¶107-108. Stahl provides a figure depicting “[s]patially localized *cDNA synthesis*,” which shows “*cDNA synthesis with Cy3-labeled nucleotides*.” EX1016, 79, FIG. 1, 78 (“[w]e used fluorescently labeled nucleotides to visualize the *synthesized cDNA*.”), Suppl. Materials, 4-5; EX1044, ¶¶107-108. Stahl’s Figure 1A depicts cDNA synthesis as red bars:



EX1016, FIG. 1A; EX1044, ¶107.

Paper 2 (“Petition”) at 26-27. As shown, Petitioner unquestionably identified cDNA synthesis with Cy3-nucleotides, as shown by the specific references to the cDNA with Cy3-nucleotides in both Stahl’s text and figure. While Petitioner points to other sections of the Petition that refer to first-strand cDNA without Cy3-

nucleotides in its Reply, Petitioner should not be allowed to cherry-pick from the Petition to piece together a coherent position when it has failed to “provide an understandable explanation of the element-by-element specifics of the patentability challenges.” *Corephotonics*, 84 F.4th at 1001.

B. Stahl Does Not Disclose Synthesizing The Claimed DNA Products

Faced with PO’s position that Petitioner failed to identify in Stahl the claimed “DNA products” because the location-identifying sequences in Stahl are not incorporated into the identified first-strand cDNAs via synthesis, Petitioner responds yet again with the misguided contention that the first-strand cDNAs meet not the claims, but merely PO’s infringement position.

Yet, Petitioner’s argument is again based on its erroneous interpretation of PO’s infringement contentions. Petitioner cannot meet its burden by relying on a position never advanced by PO.

1. The Location-Identifying Sequence Must Be Synthesized

Petitioner does not dispute that the claims require synthesis of “DNA products” that meets both a template requirement (“a synthesis reaction that uses the plurality of oligonucleotides collected in step (a) [and (b)] as templates”) and an incorporation requirement (“and incorporates at least one nucleic acid sequence that identifies the first [and second] location of the tissue sample into each of the first

[and second] plurality of DNA products”). EX1043, Claim 1(c)-(d). As PO explained, the location-identifying sequence must be incorporated in such a way that the sequence itself is synthesized. PO’s Response at 32-35.

Petitioner argues that PO’s interpretation of the incorporation requirement “is at odds with both its district court infringement interpretation, which cites Visium FF’s first-strand cDNA synthesis to meet the claimed incorporation requirement, and Dr. Sherman’s ‘single event’ interpretation.” Reply at 3. For the former, Petitioner cites to PO’s infringement contentions, where “Step 1 Permeabilization & Reverse Transcription” is listed. *Id.* at 2. It is undisputed, however, that PO’s infringement contentions include ***both steps 1 and 2*** of the Visium FF product:

c) synthesizing a first plurality of DNA products by performing a synthesis reaction that uses the plurality of oligonucleotides collected in step (a) as templates and incorporates at least one nucleic acid sequence that identifies the first location of the tissue sample into each of the first plurality of DNA products;	10x’s Visium performs a method comprising synthesizing a first plurality of DNA products by performing a synthesis reaction that uses the plurality of oligonucleotides collected in step (a) as templates and incorporates at least one nucleic acid sequence that identifies the first location of the tissue sample into each of the first plurality of DNA products. For example: <u>Visium for Fresh-Frozen:</u> Reagents are added to and reactions are performed on approximately 5000 distinct locations (gene expression spots) simultaneously. This includes, for example, that a plurality of spatially barcoded, full-length cDNAs are synthesized by performing a synthesis reaction that uses the plurality of oligonucleotides collected in step (a) as templates and incorporates at least one nucleic acid sequence that identifies the first location of the tissue sample (<i>e.g.</i>, the sequence that includes spatial barcode) into each of the first plurality of DNA products. Step 1 Permeabilization & Reverse Transcription. ... RT Master Mix containing reverse transcription reagents is added to the permeabilized tissue sections. Incubation with the reagents produces spatially barcoded, full-length cDNA from poly-adenylated mRNA on the slide. Step 2 Second Strand Synthesis & Denaturation. Second Strand Mix is added to the tissue sections on the slide to initiate second strand synthesis. This is followed by denaturation and transfer of the cDNA from each Capture Area to a corresponding tube for amplification and library construction. 10XN653-00060087 at 60102 (CG000239_Visium_Spatial_Gene_Expression_User_Guide_Rev_F at 16).
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EX1022 at 18-19. PO specifically pointed this out in its Pre-Institution Sur-Reply. See Paper 17 at 3-5. The Board similarly understood PO's infringement position: "Our interpretation on the record before us is consistent with the Specification's disclosure stated above, and also consistent with *Patent Owner's infringement contentions, where Patent Owner identifies 'synthesizing DNA products' as covering a multi-step amplification process resulting in a DNA product containing location-identifying nucleic acid sequences.*" Paper 25 at 22. Thus, Petitioner's contention that Stahl's first-strand cDNA meets PO's infringement contention is not at all aligned with PO's district court infringement position, but rather contrary to PO's district court theory.

Petitioner's reliance on Dr. Sherman's explanation that the "synthesizing" step requires "a single event," Reply at 1-2, is similarly misguided. As Dr. Sherman explained, a "single event provides that synthesis of that product, yes." EX1056 at 28:15-16. Consistent with this, PO's infringement contentions detail a collection of reactions—the first-strand and second-strand cDNA synthesis—that results in the second-strand cDNA, the claimed "DNA product." EX1022 at 18-19. Nothing in Dr. Sherman's testimony is inconsistent with this collection of related reactions in PO's infringement contentions corresponding to what a POSA might refer to as a single "event."

Petitioner also takes issue with PO's citation of the '142 patent's Figure 7 to demonstrate that a location-identifying sequence is synthesized. According to Petitioner, "Figure 7's embodiment uses a pair of ligated nucleic acid probes as the template for amplification, not the collected 'identifier oligonucleotides,' as required by claim 1." Reply at 3. Figure 7, however, depicts a collection of reactions that involve the collected oligonucleotides as templates to result in DNA products with location-identifying sequences. Petitioner, moreover, does not dispute that the location-identifying sequence depicted is synthesized, unlike the location-identifying sequence in Stahl's first-strand cDNA.

2. Petitioner Cannot Shift Theories Based On The Board's Construction

As PO explained, the Board's construction of "synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction" is erroneous because it imported embodiments into the claim by equating "synthesizing" with "amplifying," requiring at least two primers, and including an incorporation requirement of a location-identifying sequence that is recited later in the claim. PO's Response at 17-22.

In short, the Board's construction replaces the "synthesizing" in the claim with "amplifying," even though not all forms of synthesis are amplifications. *Id.* at 18-20. The Board's construction also requires at least two primers per collected

oligonucleotide during synthesis of the DNA products, despite a POSA's understanding of synthesis and amplification to include techniques with less than two primers. *Id.* at 20-21. In addition, the Board's construction requires incorporating a location-identifying sequence even though that requirement is not part of the claim term being construed and is a subsequently recited claim element. *Id.* at 21.

Petitioner does not address PO's proposed construction of plain and ordinary meaning. Furthermore, Petitioner barely addresses PO's arguments regarding the Board's construction, with the only aspect that Petitioner even attempts to defend being the Board construing "synthesizing" as "amplifying." Reply at 4. When cross-examined regarding the term "synthesizing," however, Petitioner's expert was unable to provide a clear response, stating instead that a POSA would have had difficulty interpreting the "synthesizing" term because "the infringement positions of Bruker, the IPR positions of Bruker and the Board's definition are harmonizing together to identify an interpretation of this element that is *far beyond* the plain and ordinary meaning of the terms." EX2018 at 70:4-71:8. The foregoing confirms that the Board's preliminary construction does not align with the underlying purpose of claim construction—"to give claim terms the meaning understood by a person of

ordinary skill in the art at the time of invention.” *Aylus Networks, Inc. v. Apple Inc.*, 856 F.3d 1353, 1358 (Fed. Cir. 2017).

Even if the Board maintains its preliminary construction, Petitioner should be precluded from shifting its legal theory that Stahl’s first-strand cDNA is the claimed “DNA product” to belatedly contend that Stahl’s second-strand cDNA is the claimed “DNA product.” Petitioner’s burden is proving unpatentability based on what is set out in the Petition, and Petitioner cites no law that a claim construction allows a petitioner to redo its petition to meet that burden. *See Axonics, Inc. v. Medtronic*, 75 F. 4th 1374, 1383-84 (Fed. Cir. 2023) (“We leave for another day the question of whether, when presented with a new claim construction, a petitioner can rely in its reply on new embodiments from the prior art references that were relied on in the petition.”).

Moreover, even as Petitioner attempts to shift its theory based on the Board’s construction, Petitioner continues to maintain a contrary theory by contending it “is ***undisputed*** that ***a single synthesis reaction*** meets both the template and incorporate requirements,” Reply at 1-2, in contrast to the Board’s explanation that PO’s infringement contentions describe “***a multi-step synthesis***.” Paper 25 at 22. For at least these reasons, Petitioner should not be allowed to shift its theory.

C. Stahl Does Not Disclose Amplifying A Library Using DNA Products As Templates

According to Petitioner, PO's contention that Stahl's first-strand cDNA is not used as templates to generate a library "contradicts Bruker's infringement contentions for claim 7," because the two steps listed for Visium FF do not "use the first-strand cDNAs as templates for amplification." Reply at 11-12.

Again, Petitioner reliance on PO's infringement contentions is off the mark. As discussed, PO's infringement contentions identify the second-strand cDNA in Visium FF as the claimed "DNA products." Thus, there is no contradiction—only Petitioner's mischaracterization of PO's infringement position, which cannot sustain Petitioner's burden.

Petitioner does not dispute that it identified Stahl's first-strand cDNAs as the claimed "DNA products" and that the first-strand cDNAs are not used as templates to generate a sequencing library. Even if Stahl's second-strand cDNAs were considered, they are also not used as templates. It is Stahl's second cDNA product—multiple steps removed from the first-strand cDNAs—that is amplified to add sequencing adapters and index sequences and sequenced. *See* PO's Response at 38-39. Stahl's second-strand cDNA and second cDNA product are different molecules with different sequences. *Id.* Thus, Petitioner fails to show that Stahl anticipates claim 7.

III. STAHL DOES NOT RENDER OBVIOUS CLAIMS 1-13

A. Claims 1-4, 6-13

As previously discussed, Petitioner provided no motivation to modify Stahl in its obviousness ground as to claims 1-4 and 6-13. PO's Response at 40. For the purported motivation, Petitioner states only that Stahl teaches a spatial transcriptomics method. Petition at 45.

In Reply, Petitioner states that no motivation is required because Stahl already discloses all of the required claim limitations according to PO's infringement contentions. *See* Reply at 12 ("Because Stahl discloses all the claim limitations under Bruker's infringement contentions, no further modifications are needed for a POSA to arrive at the claimed methods."). As discussed above, Petitioner fails to meet its burden that it showed that Stahl met PO's infringement contention. Moreover, as also discussed, Petitioner's contention that it met PO's infringement contentions is also erroneous.

Accordingly, if the Board finds that Ground 1 fails, such as failing to sequence the claimed "DNA products," it should likewise find that claims 1-4 and 6-13 are nonobvious.

B. Claims 5

As to claim 5, Petitioner provides only scattered arguments that fail to overcome PO's contentions that a POSA would not have been motivated or

reasonably expected to successfully modify Stahl to perform solid-phase amplification.

As an initial matter, the Petition fails to describe *how* Stahl can be modified. *See* Petition at 47 (“A POSA would have generally known that the second-strand cDNA synthesis and library amplification can be performed on Stahl’s array, *i.e.*, on the microscope slide.”). Petitioner states in its Reply for the first time that a POSA can skip the cleavage step to allow the second-strand cDNA synthesis to take place in solid-phase and that the “library amplification” refers to Stahl’s RNA amplification. Reply at 16. Yet, Petitioner never explains how the second-strand cDNA can be synthesized in solution following Stahl’s method while RNA is amplified in solid-phase. *See id.* (“perform the second-strand cDNA synthesis *and/or* library amplification on array”). This lack of disclosure is clear because even Petitioner’s expert is unable to explain the modifications to Stahl. When asked at cross-examination, Dr. Spellman states that clonal amplification “would be the most logical thing” to modify Stahl to enable solid-phase library amplification. EX2009 at 96:4-19. In his reply declaration, however, Dr. Spellman then states that “criticisms of solid-phase amplification... also fail as those criticisms are based on discussion of *colony* amplification, and not second-strand cDNA synthesis or *in vitro* transcription.” EX1055 ¶ 110.

Despite the lack of details, Petitioner contends that “assay design choices and optimizations were well within the skillset of a POSA.” Reply at 17. Petitioner cannot simply state that a POSA can figure it out. As the Federal Circuit explained:

To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness.

In re Magnum Oil Tools Int’l, Ltd., 829 F.3d 1364, 1380 (Fed. Cir. 2016). Thus, it is Petitioner’s burden to identify specific modifications to Stahl’s method. Petitioner has failed to do so here.

Petitioner also fails to establish advantages that would have motivated a POSA to modify Stahl to perform even just solid-phase second-strand synthesis. For example, Petitioner states that solid-phase amplification “significantly minimizes undesirable primer interactions,” Petition at 48, but this is no advantage because Stahl’s second-strand synthesis is conducted using random hexamers that are in solution, whether the synthesis is solid-phase or solution phase.

Contrary to Petitioner’s allegations, the improved sensitivity and selectivity of solid-phase amplification is countered by the many drawbacks of the technique, “such as electrostatic forces, the finite number of primers, polymerase and nucleotide availability, sterile molecules, and DNA stiffness can all affect the reaction.” PO’s Response at 45-46. A POSA would have been aware of these

challenges and decide against modifying Stahl to skip the cleavage step, particularly in light of Stahl's published method that, as explained by Petitioner's expert, does not perform solid-phase amplification and was "something that worked." EX2009 at 100:3-11.

Petitioner mischaracterizes PO's position as requiring certainty of advantages for a POSA to modify Stahl. As the Federal Circuit explained, "unpredictability of results equates more with nonobviousness rather than obviousness." *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1349 (Fed. Cir. 2021). Here, it is not certain whether the alleged advantages would accrue, particularly in light of the previously discussed disadvantages.

In addition, as previously explained, Frisen teaches away from solid-phase synthesis of second-strand cDNA because Frisen states that second-strand cDNA synthesis is *optional* and *preferably performed in solution*. PO's Response at 47-49. A POSA would have recognized that Frisen's inventors overlap with Stahl's authors and taken note of Stahl's lack of solid-phase amplification despite Stahl publishing years after Frisen and including stranded RNA sequencing, something not disclosed in Frisen.

Further, Petitioner contends that "the benefits from solid-phase synthesis of first-strand cDNAs and second-strand cDNAs are different and non-

interchangeable.” Reply at 19. Although the function of the two cDNA strands are different, Petitioner fails to explain why a POSA would not have understood Stahl’s solid-phase first-strand cDNA synthesis to benefit from, for example, the “improved sensitivity and selectivity” of a solid-phase reaction. Understanding that Stahl is already a working method that includes a solid-phase first-strand cDNA synthesis, a POSA would not have modified Stahl to perform solid-phase second-strand cDNA synthesis for some alleged benefits of solid-phase amplification, particularly as Petitioner points to no aspect of Stahl that requires improvement.

Accordingly, even though a POSA can modify Stahl to perform solid-phase second-strand cDNA synthesis, Petitioner has not shown that a POSA would have done so. *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (“obviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.”) (emphasis in original).

IV. SO-456 DOES NOT ANTICIPATE CLAIMS 1-13

A. So-456 Does Not Incorporate A Location-Identifying Sequence

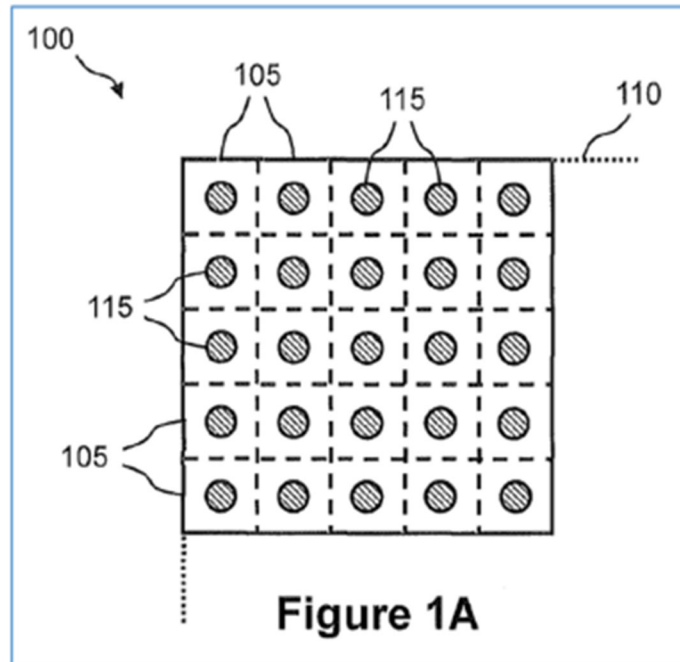
Similar to Stahl, Petitioner identified So-456’s first-strand cDNA as the claimed “DNA products”:

Q: So is it your opinion in your first declaration that the first-strand cDNAs in So-456, is the claimed DNA products of steps -- claim 1(c) and 1(d)?

A: As I believe it very clearly states there, I would -- I would agree with that statement that in paragraph 125 I identify the reverse transcribes [sic] molecule as -- as the -- as the DNA products of claim 1.

EX2018 at 62:6-14. So-456's first-strand cDNA, however, fails to (1) contain a sequence that maps back to a location of the tissue sample and (2) incorporate a location-identifying sequence by synthesis.

Petitioner's only response to the former is that "So-456's spatial address region 2325a incorporated into the first-strand cDNAs identifies the *location in the x-dimension* of the tissue sample and satisfies this claim element." Reply at 21 (emphasis in original). Petitioner does not deny, however, that So-456 defines locations on a sample as X-Y coordinates in a grid:



EX1005 Fig. 1A. Thus, the x-dimension alone is insufficient to denote a location on the tissue sample. A POSA would not understand a sequence with only the x-dimension to be a location-identifying sequence. EX2009 ¶¶ 97-102.

Regarding the lack of incorporation of the location-identifying sequence by synthesis, Petitioner again repeats its flawed mischaracterization of PO's infringement position: "Bruker's argument conflicts with its infringement contentions, which refer to Visium FF's *first-strand cDNA synthesis* for the synthesizing steps." Reply at 20 (emphasis in original). For the same reasons discussed for Stahl, however, Petitioner is wrong. See Part II.A, B.1.

Similar to Stahl, Petitioner likewise attempts to rely on the Board's construction to remedy the defect in the Petition. For the same reasons discussed for Stahl, the Board should not entertain Petitioner's argument. *See* Part II.B.2.

B. So-456 Does Not Teach Conditions That Release Oligonucleotides

Petitioner does not deny that So-456's disclosure is threadbare when it comes to "conditions that release the plurality of oligonucleotides from the first [and second] location of the tissue sample." EX1043, Claims 1(a)-(b). Petitioner, however, replies that the "Petition demonstrated that So-456 expressly and inherently teaches claim 1's condition that release oligonucleotides from a tissue sample, under Bruker's infringement contentions." Reply at 22.

Petitioner, however, is unable to identify any express teaching of the claimed "conditions" in So-456. For example, Petitioner relies on the two bolded sentences in So-456 for this express teaching:

[00152] *At a step 210, a tissue sample is prepared for analysis.* In some embodiments, the tissue sample is a FFPE tissue sample that is sectioned onto a slide. Other examples include fresh tissue, frozen tissue, etc.

[00154] *At a step 220, the target nucleic acid in the tissue section is transferred onto an array such that the position of a nucleic acid on the array can be correlated with a position in the tissue section.* In some embodiments, the target nucleic acid comprises an mRNA.

In some embodiments, the target nucleic acid comprises a cDNA synthesized in situ....

EX1005 ¶¶ 152, 154. The only technique expressly disclosed is sectioning, which is not a technique that a POSA would understand to release oligonucleotides from a sample. PO's Response at 58-59.

As to inherent disclosure, Petitioner contends that it must be present because “‘it would be *impossible*’ to analyze the nucleic acids in a tissue sample ‘without first treating the sample so that the sample nucleic acids are released.’” Reply at 23. Although Petitioner's expert lists out several techniques that he considers suitable conditions, he does not deny that they are not disclosed:

Q: In the sections in So-456, they don't mention thawing, correct?

A: I don't see a reference to thawing in So. Extensive reference to frozen tissue – several references to frozen. Paragraph 152 and paragraph 125 describe frozen samples. And obviously a frozen

sample is incapable of releasing RNA so that if -- if you were going to release it one would have to thaw it.

Q: In various sections of So-456 that you cite to they don't explicitly state the de-paraffinization, correct?

A: I do not see an explicit reference to de-paraffinization in So.

Q: Is there an explicit reference to de-crosslinking in So-456?

A: I don't believe so.

EX2018 at 153:17-154:11.

Petitioner's citation to steps in So-456 involving oligonucleotides released from the sample only highlights the lack of a working method in So-456. Although Petitioner cites to inherency to contend that the "conditions" claim element is disclosed, inherency is not a doctrine that can be twisted in such a way. Inherency comes into play when a feature is necessarily present during the practice of a prior method. Here, where So-456's method is defective because there is no disclosure of a "conditions" step or any indication that "conditions" are required to release oligonucleotides from a sample, inherency cannot be invoked to fill in the gaps of a defective disclosure to make it workable. Due to the lack of disclosure, So-456 fails to anticipate the '142 patent.

C. So-456 Does Not Disclose A Solid-Phase Amplification To Synthesize DNA Products

In response to PO pointing out that So-456's first-strand cDNA, Petitioner's identified "DNA product," does not undergo solid-phase amplification, Petitioner asserts that "Bruker's IPR position is inconsistent with its infringement contentions, which rely on Visium FF's *first-strand synthesis* to meet claim 1's synthesizing steps but Visium FF's *second-strand synthesis* to meet claim 5's solid-phase amplification step." Reply at 24 (emphasis in original). Thus, Petitioner's contention that "So-456 teaches solid-phase amplification under Bruker's infringement contentions" is again based on Petitioner's mischaracterization of PO's infringement position. As discussed throughout, PO's position is consistent.

Petitioner also contends that "claim 5's open-ended term 'comprises'" encompasses solid-phase second-strand synthesis. Reply at 24. Such a reading, however, would distort the plain language of the claim, which requires that the synthesizing steps comprise a solid-phase amplification reaction. As Petitioner notes, "So-456's solid-phase second-strand synthesis *takes place after* the first-strand cDNA synthesis." *Id.* It is not part of synthesizing the first-strand cDNAs, Petitioner's identified "DNA products." Petitioner's further reliance on the Board's construction to re-identify So-456's second-strand cDNA should not be permitted.

D. So-456 Does Not Disclose Amplifying A Library Using DNA Products

Similar to Stahl, Petitioner relies on its incorrect interpretation of PO's infringement position to allegedly satisfy claim 7:

Braker's litigation position again belies its IPR argument, because Braker's infringement contentions for claim 7 identify Visium FF's second-strand cDNA amplification (step 3) and subsequent library preparation (step 4), both of which use as templates the second-strand cDNAs, which are different from Braker's identified DNA products for claim 1's synthesis steps and have sequences "inversely complementary" to the first-strands cDNAs with additional sequences.

Reply at 26. Petitioner does not deny that it identified So-456's first-strand cDNA as the claimed "DNA products" and that So-456's first-strand cDNA is *not* used as templates to generate a sequencing library. In contrast to Visium FF, So-456's second-strand cDNA has a markedly different sequence from the first-strand cDNA due to the addition of sequencing adapters and a sequence for identifying the y-dimension. PO's Response at 61-62.

Petitioner also attempts to re-identify the "DNA products" by relying on the Board's preliminary construction of the "synthesizing" term. To the extent that construction is maintained, the Board should not permit Petitioner to remedy its flawed Petition.

V. SO-456 DOES NOT RENDER OBVIOUS CLAIMS 1-13

Similar to its obviousness ground for Stahl, Petitioner states that “[b]ecause So-456 teaches all the claim limitations under both Bruker’s infringement contentions and the Board’s and Bruker’s IPR constructions, there are no missing elements, and a POSA needed no modifications to arrive at the claimed methods.” Reply at 27. Accordingly, Petitioner confirms that its obviousness ground based on So-456 is that So-456 discloses every claim element in the ’142 patent claims, similar to Petitioner’s anticipation ground. *See id.* (“anticipation is the epitome of obviousness”). Thus, if the Board finds that Ground 4 fails, the Board should likewise find the same with Ground 5.

VI. CONCLUSION

For the going reasons, the Petition should be denied.

Dated: March 26, 2025

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 5,442 words as calculated by the “Word Count” feature of Microsoft Word 365, the word processing program used to create it.

Respectfully submitted,

JONES DAY

Dated: March 26, 2025

By: /Derek C. Walter/
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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PATENT OWNER'S SUR-
REPLY FOR INTER PARTES REVIEW OF U.S. PATENT NO. 11,473,142**
and EXHIBIT 2018 were served on March 26, 2025, via email pursuant to 37
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