

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 RESPONSE TO PETITION 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.

I. INTRODUCTION

U.S. Patent No. 11,473,142 (the “’142 patent”) is directed to an improved and novel way of spatially detecting target analytes in regions of interest. EX1043 at Abstract. The claimed methods permit the simultaneous, multiplexed detection and quantification of protein and/or nucleic acid expression in a user-defined region of a tissue, cell, and/or subcellular structure within a cell, while maintaining the morphological context of the sample. The claimed invention of the ’142 patent is an improvement over prior means of detecting target analytes in a sample, such as conventional immunohistochemical and in situ hybridization methods, which were limited to at most ten targets. *Id.* at 16:30-35. Other methods, such as laser microdissection, are limited to a small number of locations and are cost prohibitive.

Accused of infringing the ’142 patent, Petitioner now asks the Board to invalidate all 13 claims of the ’142 patent based on five grounds. These grounds, however, lack merit.

Grounds 1, 2, and 3 all rely on a reference by Stahl et al. (“Stahl”). *See* EX1016. These grounds—whether based on anticipation or obviousness—necessarily fail, because Stahl does not disclose or render obvious at least independent claim 1, from which claims 2-13 depend. Specifically, Petitioner fails to show that Stahl discloses or renders obvious at least two claim elements in claim

1. Stahl does not sequence Petitioner's identified DNA product (a first-strand cDNA), and instead sequences a distinctly different molecule (a second cDNA product with a completely different sequence). Stahl likewise does not synthesize Petitioner's identified DNA products by incorporating a location-identifying sequence by synthesis.

While Petitioner's failure to meet its burden on independent claim 1 is more than sufficient for the Board to uphold the claims, Petitioner likewise fails to demonstrate why a person of ordinary skill in the art would modify Stahl, alone or in combination with Frisen, to perform solid-phase amplification, as required by dependent claim 5. In addition, Petitioner fails to show that Stahl discloses amplifying a library using Petitioner's identified DNA products as templates, required by claim 7, as Petitioner's identified amplification reaction involves other molecules as templates.

Grounds 4 and 5 rely on a reference by So et al. ("So-456"). EX1005. These grounds also fail, as So-456 does not disclose or render obvious at least five claim elements across the independent and dependent claims.

Three required claim elements in independent claim 1 are missing. Petitioner's identified DNA products in So-456 do not incorporate a complete location-identifying sequence. Like Stahl, Petitioner's identified DNA products in

So-456 do not incorporate a location-identifying sequence during synthesis. In addition, So-456 does not disclose conditions that release oligonucleotides from a tissue sample.

At least two claim elements in the dependent claims are undisclosed. So-456 does not disclose a solid-phase amplification during synthesis of Petitioner's identified DNA products, as required by claim 5. So-456 also does not disclose amplifying a library using Petitioner's identified DNA products as templates, as required by claim 7.

Petitioner fails to meet the burden of demonstrating by a preponderance of the evidence that any of the '142 Patent claims are invalid, as detailed herein and supported by the declaration of Dr. David H. Sherman (EX2008). The Board should accordingly find in Patent Owner's favor.

II. BACKGROUND

A. The '142 Patent

The '142 Patent is directed to a method of spatially detecting target analytes in regions of interest. EX2008 ¶¶ 36-39. This method can detect and quantify proteins and/or nucleic acids from particular locations in a tissue sample. Specifically, the '142 Patent relates to “probes, compositions, methods, and kits for simultaneous, multiplexed detection and quantification of protein and/or nucleic acid

expression in a user-defined region of a tissue, user-defined cell, and/or user-defined subcellular structure within a cell that are adaptable for use with existing sequencing technologies.” EX1043 (’142 Patent) at Abstract.

Claim 1 recites:

1. A method comprising:

- a) collecting a plurality of oligonucleotides from a first location of a tissue sample under conditions that release the plurality of oligonucleotides from the first location of the tissue sample;
- b) collecting a plurality of oligonucleotides from a second location of the tissue sample under conditions that release the plurality of oligonucleotides from the second location of the tissue sample;
- 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;
- d) synthesizing a second plurality of DNA products by performing a synthesis reaction that uses the plurality of oligonucleotides collected in step (b) as templates and incorporates at least one nucleic acid sequence that identifies the second location of the tissue sample into each of the second plurality of DNA products; and
- e) identifying the first plurality of DNA products and the second plurality of DNA products synthesized in step (c) and step (d) by sequencing the first plurality of DNA products and the second plurality of DNA products, thereby spatially detecting the plurality of oligonucleotides collected from the first location of the tissue sample and the plurality of oligonucleotides collected from the second location of the tissue sample.

Id. Claim 1.

The claimed methods are directed to the spatial detection of target analyte in a first and second location of a tissue sample. At a high level, the method involves collecting oligonucleotides from a first and second location of a tissue sample, performing a synthesis reaction on the collected sample oligonucleotides to incorporate a nucleic acid sequence that identifies a location, and identifying the location of the extension products via sequencing. Claims 2-13 depend on claim 1.

The '142 Patent was issued on October 18, 2022, from U.S. Patent Application No. 17/476,712 ("’712 Application"), filed on September 16, 2021. The '712 Application is a continuation of U.S. Patent Application No. 16/272,487 ("’487 Application"), filed February 11, 2019, which claims priority to U.S. Provision Applications Nos. 62/629,180, filed February 12, 2018, and 62/771,212, filed November 26, 2018. The specification of the '712 Application and the '487 Application are identical.

B. The Level Of Ordinary Skill In The Art

A person having ordinary skill in the art ("POSA") relevant to the '142 patent as of February 11, 2019, would have had a Ph.D. in molecular biology, genetics, chemistry, biochemistry, organic chemistry, microbiology, or a related discipline, with at least two years of experience in the spatial detection of proteins and nucleic

acids. EX2008 ¶¶ 19-21. Alternatively, a POSA would have been someone with greater relevant experience sufficient to compensate for having less relevant formal education. *Id.*

A POSA would have understood at least the following technologies and techniques:

- Phosphoramidite chemistry;
- Ligase chain amplification;
- Rolling circle amplification;
- Stranded RNA sequencing.

EX2008 ¶ 22.

C. Petitioner's References

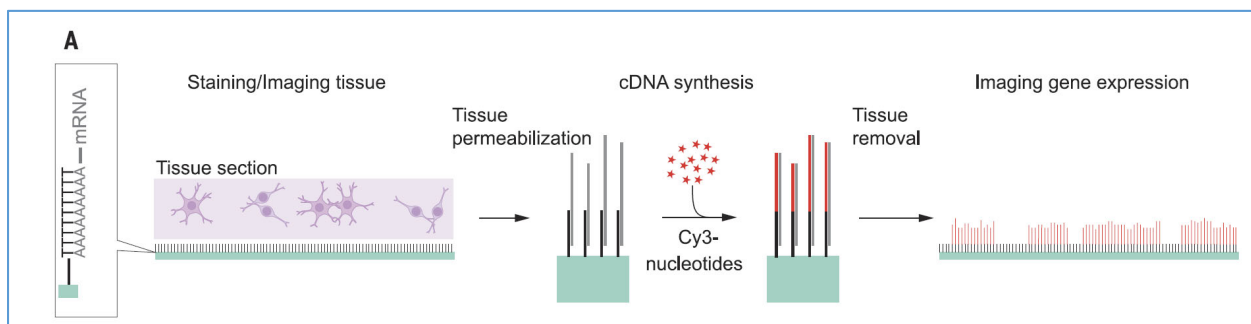
The Petition cites three references. A summary of each reference is provided below as relevant background.

1. Stahl

Stahl is a scientific publication entitled “Visualization and analysis of gene expression in tissue sections by spatial transcriptomics” that published in 2016. EX1016. The article purports to describe using “arrayed reverse transcription primers with unique positional barcodes” to capture oligonucleotides on the surface of microscope glass slides. *Id.* at 78. Upon placing sections of tissue on the

arrays and permeabilizing the tissue, mRNA from the tissue migrates from the tissue to the array and is captured by the capture oligonucleotides. “RNA-sequencing data with maintained two-dimensional positional information from [] mouse brain and human breast cancer” were then collected to allow “quantitative gene expression data and visualization of the distribution of mRNAs within tissue sections.” *Id.* Additional detail on Stahl’s method is set forth below.

After RNA from the tissue is captured on the array, Stahl teaches a reverse transcription step to synthesize cDNA from messenger RNA (mRNA) in the tissue sections on a surface. *Id.* For this purpose, Stahl uses “immobilized reverse-transcription oligo(dT) primers on glass slides” placed on the slides sections of the sample tissue. *Id.* The tissue is “fixed, stained and imaged.” *Id.* Figure 1A illustrates the cDNA synthesis:



Id. Fig. 1A. As the figure shows, the reverse transcription reaction incorporates the cDNA sequence (shown in red) to the reverse-transcription oligo(dT) primer/surface probe (shown in black) using the sample mRNA (shown in grey) as a template. The

surface probe contains “a cleavage site, a T7 amplification and sequencing handle, a spatial barcode, a unique molecular identifier (UMI), and an oligo(dT) VN-capture region.” *Id.* at 80. The reverse transcription reaction does not incorporate the spatial barcode, which is already present in the surface probe, is not synthesized, and is otherwise passive during the synthesis reaction.

After the synthesis reaction that resulted in the first cDNA products, cleavage of the surface probe releases the first cDNA products. *See* EX1016, Suppl. Materials at 6. Subsequently, second-strand cDNA molecules are synthesized in solution and are further cleaned up to generate amplified RNA via transcription by T7 RNA polymerase. *Id.* Thereafter, ligation adapters are appended to the amplified RNA and single-stranded cDNA molecules are generated from the amplified RNA. *Id.* at 6-7. These single-stranded cDNA products are then sequenced to analyze the visualization and quantitative analysis of the tissue transcriptome. *Id.*

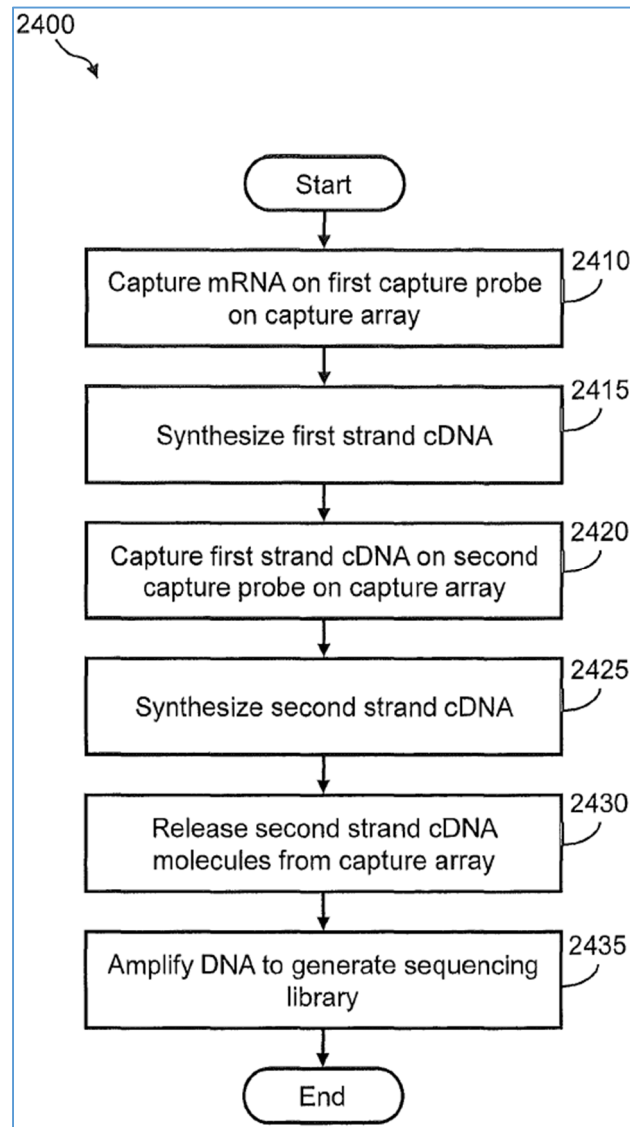
As documented further herein, Stahl fails to disclose several key features of the '142 Patent claims. In particular, Petitioner fails to show that Stahl discloses identifying the DNA products by sequencing them, a synthesis reaction to incorporate a spatial barcode, amplifying DNA products as templates to generate a

library, or synthesizing DNA products via a solid-phase amplification reaction, in a way that maps to the claims as drafted.

2. So-456

So-456 is a PCT application entitled “Spatial Mapping of Nucleic Acid Sequence Information” that published on February 2, 2017, as No. WO2017/019456. EX1005 (“So-456”). So-456 purports to provide “methods and compositions for spatial detection and analysis of nucleic acids in a tissue sample.” *Id.* at Abstract. So-456, however, is a speculative patent application that describes an incomplete method.

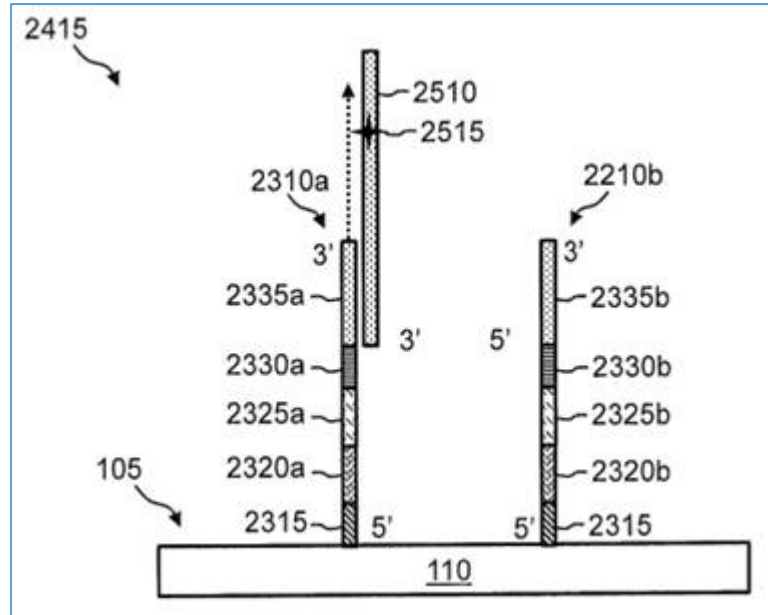
The relied upon method in So-456 is set forth in Figure 24:



Id. Fig. 24. As an initial step, mRNA in a tissue sample is supposedly captured on a capture probe. *See id.* ¶ [00315]. So-456, however, does not provide any detail or explanation as to how mRNA is released from a tissue sample for this capture.

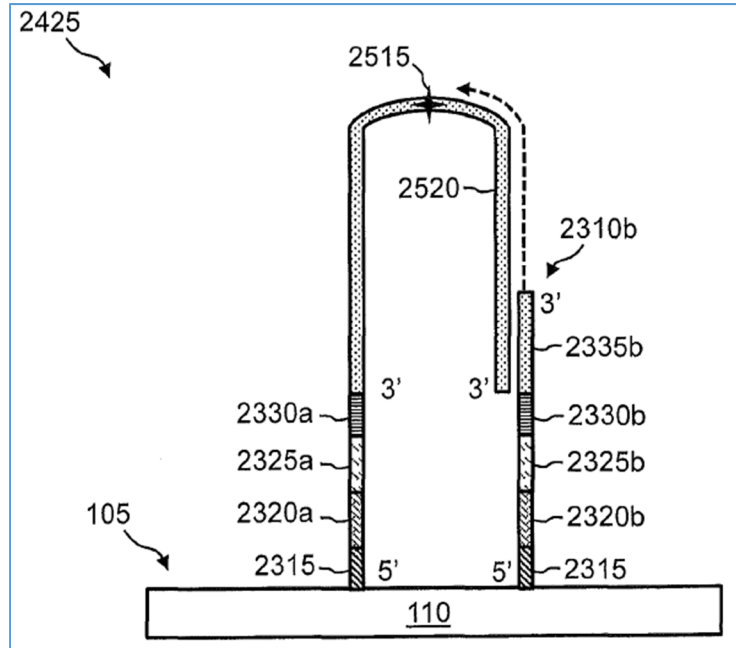
The capture probe contains a spatial barcode sequence, a sequencing primer, and an optional cleavable region. *Id.* Fig. 25A, ¶ [00302]. So-456 describes

immobilizing the capture probes “such that a 3’-end is available for enzymatic extension.” *Id.* ¶ [00109]. Synthesis of the first strand cDNA is depicted in Figure 25A:



Id. Fig. 25A. Thus, the synthesis reaction taught by So-456 incorporates the target analyte sequence onto a capture probe that already contains a SBS primer sequence and a spatial address region. The extension taught by So-456 does not incorporate any nucleic acid sequence that identifies the location of the tissue sample because any such sequence that might serve such a function was present in the capture probe and is completely passive with respect to the extension reaction.

Following the extension reaction, the 3' end of the first strand cDNA molecule is captured on an adjacent capture probe. *Id.* ¶ [00317]. A second strand is subsequently synthesized:



Id. Fig. 25B, ¶ [00318]. This second strand cDNA molecule has a different sequence than the first strand cDNA molecule. The second strand cDNA molecule is released into solution via cleavage of a cleavage region. *See id.* ¶ [00319]. Subsequent amplification of the second strand cDNA molecule incorporates sequences necessary for sequencing. *See id.* ¶ [00320]. The final product is sequenced and the sequencing data is analyzed “to provide information as to the location of the nucleic acid in the tissue section.” *Id.* ¶¶ [00156]-[00158].

As documented further herein, Petitioner fails to show that So-456 discloses several key features of the '142 Patent claims, including performing a synthesis reaction to incorporate a spatial barcode, identifying the DNA products by sequencing the first strand cDNA products, or conditions wherein mRNA are released from a tissue sample.

3. Frisen

Frisen is a PCT application entitled “Method And Product For Localised Or Spatial Detection Of Nucleic Acid In A Tissue Sample” that published on October 18, 2012 as WO2012/140224. EX1017. Frisen purports to provide “methods and products for the localised or spatial detection of nucleic acid in a tissue sample”:

The present invention relates to methods and products for the localised or spatial detection of nucleic acid in a tissue sample and in particular to a method for localised detection of nucleic acid in a tissue sample comprising: (a) providing an array comprising a substrate on which multiple species of capture probes are directly or indirectly immobilized such that each species occupies a distinct position on the array and is oriented to have a free 3' end to enable said probe to function as a primer for a primer extension or ligation reaction, wherein each species of said capture probe comprises a nucleic acid molecule with 5' to 3': (i) a positional domain that corresponds to the position of the capture probe on the array, and (ii) a capture domain; (b) contacting said array with a tissue sample such

that the position of a capture probe on the array may be correlated with a position in the tissue sample and allowing nucleic acid of the tissue sample to hybridise to the capture domain in said capture probes; (c) generating DNA molecules from the captured nucleic acid molecules using said capture probes as extension or ligation primers, wherein said extended or ligated DNA molecules are tagged by virtue of the positional domain; (d) optionally generating a complementary strand of said tagged DNA and/or optionally amplifying said tagged DNA; (e) releasing at least part of the tagged DNA molecules and/or their complements or amplicons from the surface of the array, wherein said part includes the positional domain or a complement thereof; and (f) directly or indirectly analysing the sequence of the released DNA molecules.

Id. at Abstract. In particular, Frisen discloses that, after DNA molecules have been generated on capture probes, a complementary strand of the DNA can be optionally generated or the DNA can be optionally amplified. *Id.*

III. CLAIM CONSTRUCTION

In concurrent litigation, the parties agreed that “spatially detecting” should be construed as “identifying the presence of a specific target analyte within a specific region of interest in a sample.” EX1052 at 42. In addition, the district court construed the terms “under conditions that release” and “first/second location of the tissue sample” to have their plain and ordinary meaning. *Id.* at 38, 41.

The Board, in the Decision Granting Institution, construed or interpreted the following terms:

- “identifying a first plurality [and second plurality] of DNA products by sequencing” – “locating the specific target analyte within the tissue sample by correlating the DNA product using the location-identifying nucleic acid sequences.” Paper 25 at 26-28.
- “synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction” – “amplifying the collected plurality of oligonucleotides released after application of a force from the location of the sample using primers that 1) have binding sites on the collected oligonucleotide and 2) contain location-identifying nucleic acid sequences that are incorporated into the DNA product upon synthesis.” *Id.* at 19-22.

Patent Owner disagrees with the Board’s preliminary constructions and states the basis for its disagreement herein. EX2008 ¶¶ 23-35.

A. Identifying the first plurality of DNA products and the second plurality of DNA products synthesized in step (c) and step (d) by sequencing

The Board’s preliminary construction of “identifying a first plurality [and second plurality] of DNA products by sequencing” removes a critical aspect of the claim step wherein the “identifying” is performed “by sequencing.” As Dr. Sherman explains, “sequencing” is a common term that a POSA would understand in the context of the ’142 patent to mean determining the sequence of a nucleic acid. The Board’s construction obviates the requirement to sequence the DNA products. EX2008 ¶¶ 26-28.

The claim language is clear that this “identifying” step is performed “by sequencing.” *Id.* ¶ 29. The Board’s preliminary construction, however, merely requires “locating the specific target analyte...by correlating....” Thus, Patent Owner disagrees with the Board’s preliminary construction, which reads out the claim requirement that sequencing is the recited method for identifying the DNA products. Even though the parties agreed in a parallel proceeding to the construction of “spatially detecting,” the parties did not agree that sequencing was not a required claim element. As the claims recite, the “the first plurality of DNA products and the second plurality of DNA products” must be sequenced. EX1043 Claim 1(e).

Accordingly, Patent Owner proposes the plain and ordinary meaning for the claim term “identifying the first plurality of DNA products and the second plurality of DNA products synthesized in step (c) and step (d) by sequencing.” To the extent the Board finds that construction is necessary to resolve the present dispute, Patent Owner proposes “locating the specific target analyte within the tissue sample by correlating the DNA product using the location-identifying nucleic acid sequences, wherein the sequence of the DNA product and the sequence of the location-identifying nucleic acid sequences are determined via sequencing.” EX2008 ¶ 29.

B. Synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction

The Board’s preliminary construction of “synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction” (1) equates “synthesizing” and “amplifying;” and (2) requires at least two primers for each collected oligonucleotide; and (3) requires “location-identifying nucleic acid sequences that are incorporated into the DNA product upon synthesis.” Patent Owner submits that each of these three requirements are erroneous and that the plain and ordinary meaning of the term should be adopted. EX2009 ¶¶ 30-35.

The Board’s preliminary construction was based almost exclusively on a single passage from column 11 of the specification about what the “present disclosure provides.” *See* Paper 25 at 20-21. Yet, the ’142 specification includes roughly 36 passages describing various things that the “present disclosure provides.” The Board, in its institution decision, picked one of these passages about a particular embodiment and made it the basis for its claim construction, which, as a result, includes several erroneous limitations. *See id.*

For example, the Board’s preliminary construction included specific limitations from the embodiment at column 11, such as “amplifying the plurality of oligonucleotides,” “application of a force,” “using primers that have binding sites on the collected oligonucleotide,” and “location-identifying nucleic acid sequences that

are incorporated into the DNA product upon synthesis.” As the Federal Circuit has explained, one should “depart from the plain and ordinary meaning of claim terms based on the specification in only two instances: lexicography and disavowal.” *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1371 (Fed. Cir. 2014). The Board’s institution decision pointed to neither lexicography nor disavowal as a basis for deviating from the plain and ordinary meaning of the claim term. It “is the *claims*, not the written description, which define the scope of the patent right.” *Laitram Corp. v. NEC Corp.*, 163 F.3d 1342, 1347 (Fed. Cir. 1998) (emphasis in original).

By failing to heed these principles and construing the claims in the manner that it did, the Board improperly “read[s] limitations from the embodiments in the specification into the claims.” *Hill-Rom*, 755 F.3d at 1371 (“While we read claims in view of the specification, of which they are a part, we do not read limitations from the embodiments in the specification into the claims.”). Pursuant to the Board’s construction, at least three unwarranted limitations have been imported into the claims.

First, the Board’s construction of “synthesizing” to mean “amplifying” is contrary to a POSA’s understanding of these terms. As Dr. Sherman explains, synthesis in the context of nucleic acids refers to the generation of a nucleic acid

strand, whereas amplification refers to generating copies of a specific nucleic acid. EX2008 ¶ 31. Dr. Spellman, Petitioner's expert, agrees that amplification reactions are a subset of synthesis reactions. EX2009 at 28:3-31:2. For example, Dr. Spellman specifically notes that phosphoramidite chemistry is a type of synthesis that is not amplification:

Q Let's put it this way: Are there synthesis reactions that are not amplification reactions?

A Yes.

Q Can you provide an example?

A The trivial one of using phosphoramidite chemistry to make a chain of nucleic acids from scratch.

Id. at 29:19-30:4; EX2008 ¶ 31. Dr. Spellman further agreed that the claims reciting "synthesizing" are not limited "amplifying":

Q Do you agree that Claim 1 is not limited to amplification reactions to synthesized DNA products?

A You're asking whether or not the reaction in C and D, it does not have to be an amplification reaction. Correct?

Q Correct, that was the question. Yes.

A That's correct.

EX2009 at 57:8-16. Petitioner's own expert thus confirms that the Board's construction is incorrect.

The claim language itself confirms that this term, which refers only to “synthesizing,” cannot be limited to “amplification.” EX2008 ¶ 32. Claim 5, which depends from claim 1, includes the additional limitation of “performing a solid-phase amplification” when synthesizing DNA products. Following claim differentiation, “synthesizing” must encompass more than simply “amplifying,” as the Board preliminarily concluded.

Second, the Board’s preliminary construction requires plural “primers that have binding sites on the collected oligonucleotide,” such that the synthesis of each DNA product must involve at least two primers. EX2008 ¶ 33. While the ’142 patent, as noted by the Board, includes an embodiment in which a collected oligonucleotide is amplified “using a first amplification primer capable of binding to the first amplification primer binding site and a second amplification primer capable of binding to the second amplification primer binding site,” Paper 25 at 20, that is simply an *embodiment* and the claims should not be accordingly restricted. *See Hill-Rom*, 755 F.3d at 1371. As Dr. Sherman explains, a POSA would have understood synthesis to comprise any available method, including those where less than two primers are involved, such as phosphoramidite synthesis, discussed above. EX2008 ¶ 33. Even for amplification methods, examples exist such as ligase chain

reaction (involving no primers) and rolling circle amplification (involving a single primer). *Id.*

Third, the Board’s construction requires “location-identifying nucleic acid sequences” to be incorporated into the DNA product. *Id.* ¶ 34. Although the claim step contains such a requirement, that is a separate limitation recited later in claim 1(e) and should not be part of the construction of “synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction,” as “[c]onstruing a claim term to include features of that term already recited in the claims would make those expressly recited features redundant:”

The Board was correct to not include in its construction of “menu” features of menus that are expressly recited in the claims. Ideally, claim constructions give meaning to all of a claim’s terms. *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005). Construing a claim term to include features of that term already recited in the claims would make those expressly recited features redundant.

Apple, Inc. v. Ameranth, Inc., 842 F.3d 1229, 1237 (Fed. Cir. 2016). Since a later cited limitation already includes incorporating the location-identifying sequence into the DNA products during synthesis, this limitation should not be part of the construction of “synthesizing...DNA products by performing a synthesis reaction.”

As Dr. Sherman explains, a POSA would have understood the term “synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction” to have a plain and ordinary meaning. EX2008 ¶ 35. The language of the claim term requires performing a synthesis reaction to generate DNA products. Additional limitations in the claim step qualifies the synthesis reaction by requiring (1) the collected oligonucleotides to be used as templates and (2) the location-identifying sequences to be incorporated into the DNA products. Nothing more is needed to interpret the claim term.

For at least the above reasons, the plain and ordinary meaning should be adopted.

IV. 10X GENOMICS HAS NOT SHOWN UNPATENTABILITY OF THE CHALLENGED CLAIMS

A. GROUND 1: STAHL DOES NOT ANTICIPATE CLAIMS 1-4, 6-13

Petitioner argues that Stahl anticipates claims 1-4 and 6-13 of the '142 Patent, including independent claim 1. “Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim.” *Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd.*, 807 F.3d 1283, 1293 (Fed. Cir. 2015) (citation omitted). Here, Petitioner fails to meet this standard. Specifically, Petitioner fails to show that Stahl discloses (1) sequencing DNA

products; (2) synthesizing DNA products that incorporate a nucleic acid sequence that identifies location; and (3) amplifying a library using DNA products as templates. Because Stahl fails to disclose at least these elements, it does not anticipate claims 1-4 and 6-13 of the '142 Patent. EX2008 ¶¶ 40-65.

1. Stahl Does Not Disclose Sequencing DNA Products

Stahl does not disclose the “identifying” step of independent claim 1, from which claims 2-13 depend. EX2008 ¶¶ 41-49. Claim 1 first requires “synthesizing a first [and second] plurality of DNA products by performing a synthesis reaction that uses the plurality of oligonucleotides collected in step (a) as templates.” EX1043 Claim 1(c), 1(d). Subsequently, these “DNA products” are sequenced to identify them:

e) identifying the first plurality of DNA products and the second plurality of DNA products synthesized in step (c) and step (d) by *sequencing the first plurality of DNA products and the second plurality of DNA products*, thereby spatially detecting the plurality of oligonucleotides collected from the first location of the tissue sample and the plurality of oligonucleotides collected from the second location of the tissue sample.

Id. Claim 1(e).¹ Thus, to satisfy this “sequencing DNA products” claim element, Petitioner must identify the synthesized “DNA products” in Stahl and show that these “DNA products” are sequenced. Petitioner cannot make this showing.

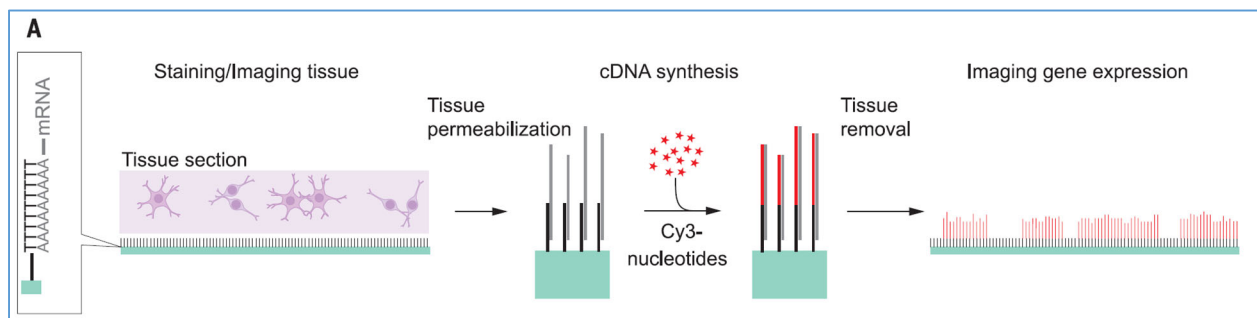
In Stahl, mRNA in the tissue is hybridized via a poly-A tail to the complementary poly-T region of capture probes—oligonucleotides that are attached to a microscope slide. EX2008 ¶ 42. Subsequently, reverse transcription occurs wherein the capture probes are extended to include a sequence complementary to the hybridized mRNA. *Id.*

Petitioner identifies “a reverse transcription reaction to ‘synthesize’ cDNA products using the captured mRNAs as templates” as meeting the claim element of “synthesizing a first [and second] plurality of DNA products by performing a synthesis reaction that uses the plurality of oligonucleotides collected in step (a) as templates.” Paper 2 at 26-27. Petitioner explains that “Stahl’s synthesis reactions use the first and second plurality of oligonucleotides (mRNAs) collected in steps (a) and (b) (respectively) as templates, because Stahl uses reverse transcription to synthesize a ‘complementary’ DNA, *i.e.*, cDNA, strand using the captured mRNA as a template.” *Id.* at 27. Thus, Petitioner identifies the first-strand cDNA—*i.e.*,

¹ Emphasis added throughout unless otherwise noted.

the product of the reverse transcription reaction—as the claimed “DNA products” in Stahl. EX2008 ¶ 43.

Petitioner further identifies the “*cDNA synthesis* with Cy3-labeled nucleotides,” specifically citing “fluorescently labeled nucleotides to visualize the *synthesized cDNA*” in Stahl. Paper 2 at 26 (emphasis in original). As support, Petitioner points to the “cDNA synthesis as red bars” in Figure 1A, reproduced below:



EX1016 Fig. 1A; Paper 2 at 26-27. Petitioner’s expert, Dr. Spellman, likewise agrees. EX1044 ¶¶ 107-108; EX2008 ¶ 44. Accordingly, the red bars depicted in Figure 1A are the synthesized cDNA that Petitioner identifies as the claimed “DNA products.” *Id.*

As the Supreme Court stated, “the petitioner’s contentions, not the Director’s discretion, define the scope of the litigation all the way from institution through to conclusion.” *SAS Inst., Inc. v. Iancu*, 584 U.S. 357, 367 (2018). The Federal Circuit has further explained that the “IPR petition, thus, 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 clearly identifies the red bar in Figure 1A, the synthesized portion of the first-strand cDNA with Cy3-nucleotides, as the claimed “DNA products.” EX2008 ¶¶ 43-44. Due to this identification, Petitioner has the burden to show how Stahl meets each claim limitation that requires “DNA products.”² While Petitioner may argue that Patent Owner identified a second-strand cDNA as the “DNA products” in its infringement contentions in a parallel proceeding, Petitioner cites no authority that Petitioner may change “the identification of particular portions of prior art on which the petitioner is relying” after a petition has

² In the institution decision, the Board noted that it “interpret[ed] ‘synthesizing DNA products’ *not* to require direct replication of the first cDNA strand – and only this strand – to create the end product, as Patent Owner urges.” Paper 25 at 22 (emphasis in original). Regardless of the method in Stahl, Petitioner’s identification of the red bar in Figure 1A as the “DNA products,” the synthesized cDNA with Cy3-nucleotides, is the evidence in the Petition. Petitioner never pursued any invalidity theory that was not based upon direct replication of the first cDNA strand in Stahl. As such, to the extent there is potentially some disclosure in Stahl that supports an indirect theory, it is irrelevant for the purposes of these proceedings. *See* 35 U.S.C. § 312(a)(3) (“the petition identifies, in writing and with particularity...the evidence that supports the grounds for the challenge to each claim”).

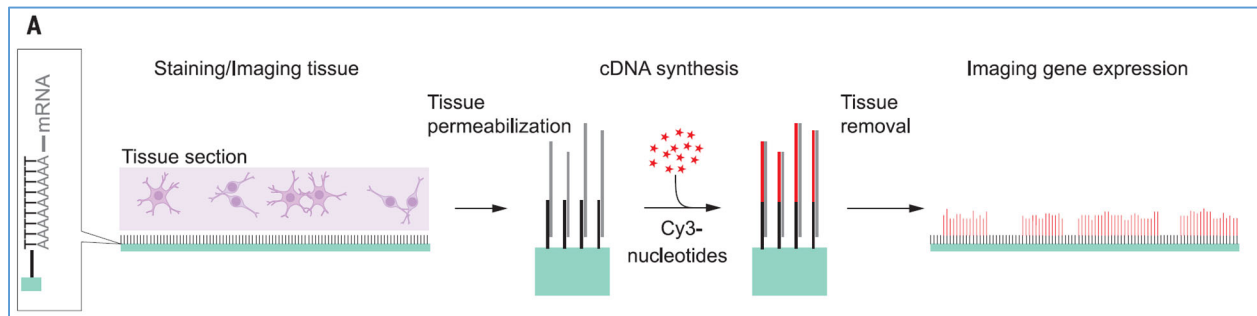
been filed, particularly as Petitioner was in possession of the contentions prior to the filing of the petition and cites it throughout the petition. *See Corephotonics*, 84 F.4th at 1001.

Claim 1 requires “sequencing the first plurality of DNA products and the second plurality of DNA products.” EX1043 Claim 1(e). Petitioner devotes only one sentence of its Petition to attempt to show that the synthesized portion of the first-strand cDNA it identified as the claimed “DNA products” is sequenced:

After synthesizing the cDNA products (first and second plurality of DNA products) on the array, Stahl discloses generating “sequencing libraries” by collecting the spatially barcoded cDNA synthesis products, amplifying them, and sequencing the amplified library “on the Illumina NextSeq platform using paired-end sequencing according to the manufacturer’s protocol.”

Paper 2 at 30. Petitioner’s identified “DNA products,” however, are *not* sequenced.

As an initial matter, Stahl does not sequence the synthesized cDNA containing Cy3-nucleotides or any of its downstream products. EX2008 ¶ 44. After cDNA with Cy3-nucleotides is synthesized, the array is imaged and subsequently discarded:

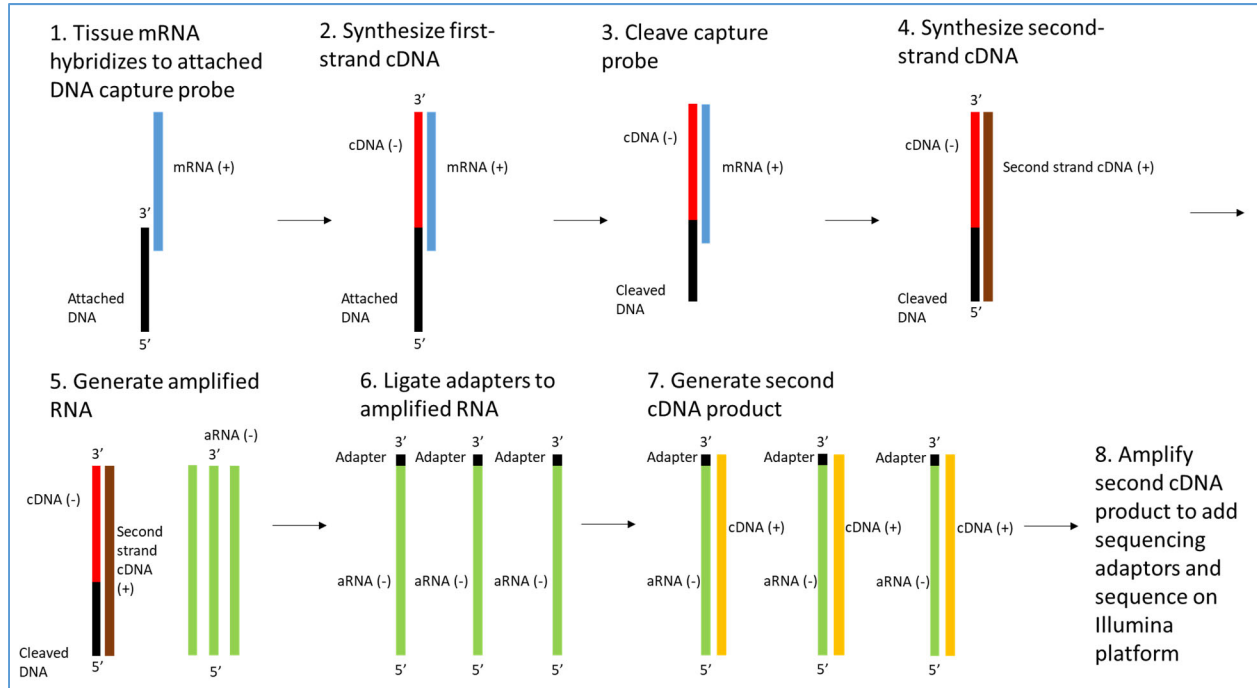


EX1016 Fig. 1A. The cDNA with Cy3-nucleotides is not cleaved and used in subsequent steps in Stahl's workflow. Instead, it is cDNA *without* Cy3-nucleotides that proceeds within Stahl's workflow which leads to sequencing of a different cDNA product. This is evident as Stahl describes one workflow for sequencing and one workflow for imaging. Only the imaging workflow incorporates Cy3-nucleotides, which Petitioner identified as the claimed "DNA products":

For spatially barcoded arrays belonging to samples *intended for sequencing*, the reverse transcription mix contained 1x First Strand Buffer (#18080-044, Invitrogen)...500μM of each dNTP (#R0192, Fisher Scientific)...For spatially barcoded arrays and surfaces with poly-T reverse transcription primer *intended for generation of fluorescent cDNA footprints*, the reverse transcription mix contained the same reagents as above except for...**25μM of Cyanine 3-dCTP** (#NEL576001EA, PerkinElmer).

EX1016, Suppl. Materials at 5; EX2008 ¶ 44.

Even if Petitioner identified the first-strand cDNA *without* Cy3-nucleotides, Stahl's method sequences a completely different molecule, a second cDNA. EX2008 ¶¶ 45-47. Stahl's process is depicted below:



Id. ¶ 46. After first-strand cDNA is synthesized from reverse transcription (depicted in red), the DNA-RNA strand is cleaved and released into solution. *Id.* Next, while in solution, the mRNA (depicted in blue) is degraded and a complementary cDNA second strand (depicted in brown) is formed, creating a DNA-DNA duplex. *Id.* Then, amplified RNA (depicted in green) is synthesized from the second-strand cDNA. *Id.* Subsequently, adaptors (depicted in black) are ligated to one end of the amplified RNA before the amplified RNA is reverse transcribed into cDNA (depicted in orange). *Id.* As Dr. Sherman explains, Stahl

sequences this second cDNA product (depicted in orange) using next-generation sequencing, not the synthesized first-strand cDNA (depicted in red). *Id.* Petitioner's expert likewise agrees that it is the second cDNA product that is sequenced on an Illumina platform:

Q Let's skip the next sentence and to the one after it, which starts with, "After determining the amount of cycles needed based on the qPCR, the samples were amplified in a total reaction volume of 25 microliter." Do you see that?

A Yes.

Q Do you agree that the cDNA is being amplified in this step?

A Yes.

Q And if you read through the rest of this section, do you agree that the amplified cDNA is then sequenced on an Illumina NextSeq platform?

A Yes.

EX2009 at 75:16-76:8 (objection omitted).

Furthermore, in addition to Stahl sequencing a molecule that is neither a first-strand cDNA nor a first-strand cDNA containing Cy3-nucleotides, the sequenced second cDNA product (depicted in orange) possesses a different sequence. As Dr. Sherman explains, the process in Stahl shows a deliberate effort by Stahl to preserve

and determine the exact sequence of the captured mRNA.³ *Id.* ¶ 47. Stranded RNA sequencing is a concept well-known in the art to achieve what Stahl demonstrated, determining the exact sequence of mRNA molecules and not their complement. *Id.* A POSA would have known that accurate quantitative expression data requires stranded RNA sequencing. *Id.*

Rather than sequence the first-strand/second-strand cDNA (depicted in step 4 above), Stahl intentionally teaches stranded RNA sequencing to preserve the strand specificity of the captured sample mRNA. *Id.* Stahl achieves this by generating amplified RNA with an adapter on only its 3' end, allowing the directionality of the sequencing data to be determined. *Id.* Thus, Petitioner's contention that a first-strand cDNA is sequenced is contrary to Stahl's teachings and negates Stahl's intentional application of stranded RNA sequencing. *Id.* As Dr. Sherman explains, Petitioner's contention is an obfuscation of Stahl's workflow. *Id.* ¶ 48.

Accordingly, Petitioner fails to show that Stahl anticipates the claims of the '142 patent at least because Petitioner's identified "DNA products" is not sequenced.

³ Stahl deliberately transcribes the first-strand/second-cDNA duplex into amplified RNA before reverse transcribing back into a single-stranded cDNA that has the same orientation and sequence as the initial captured mRNA. This technique of strand preservation allows more accurate transcript expression levels to be detected as many genetic loci are transcribed from both directions. Thus, maintaining the strand origin is vital to accurately determine expression levels.

2. Stahl Does Not Disclose A Synthesis Reaction That Incorporates A Nucleic Acid Sequence That Identifies Location

Stahl does not disclose the “synthesizing” steps in independent claim 1, from which the other claims depend. EX2008 ¶¶ 50-56. Claim 1 requires “a synthesis reaction that...incorporates at least one” spatial barcode:

synthesizing a first [and second] plurality of DNA products by *performing a synthesis reaction that* uses the plurality of oligonucleotides collected in step (a) [and (b)] as templates 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), 1(d).

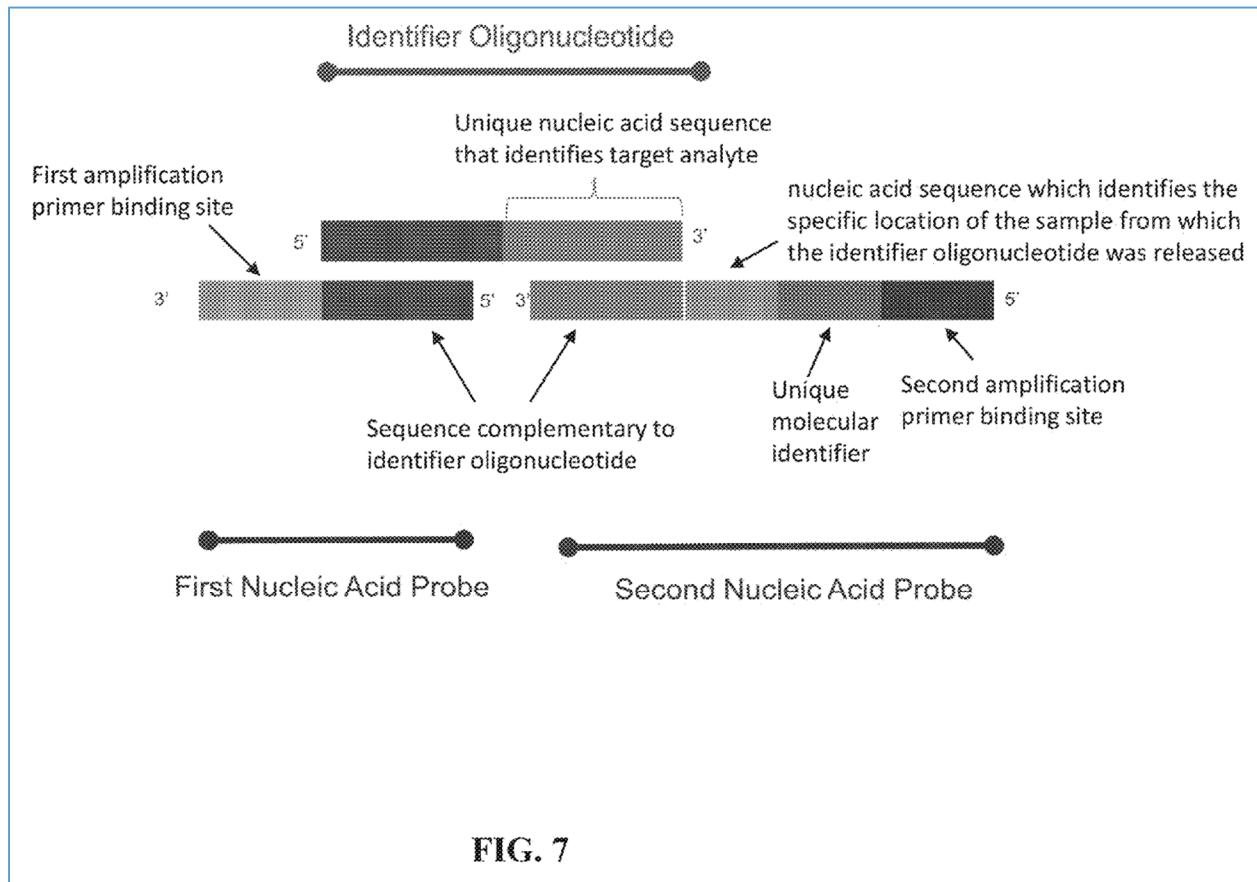
As discussed above, the plain and ordinary meaning of this term should be adopted. *See supra* § III.B. According to the claims, “DNA products” must be synthesized “by performing a synthesis reaction that...incorporates at least one” spatial barcode. *Id.*; EX2008 ¶ 51. Thus, the incorporation of the location-identifying sequence must be part of the synthesis reaction that takes place to synthesize “DNA products.”

Usage of the claim term “incorporate” is consistent with this interpretation. A POSA would have understood “incorporate” to mean the synthesis of each nucleotide of the location-identifying sequence as it becomes part of the “DNA

products,” as that is the common usage of the term “incorporate” in the context of DNA synthesis. EX2008 ¶ 52.

The specification supports such an interpretation. EX2008 ¶ 53. For example, the specification includes phrases such as “incorporating one or more nucleotides into a polynucleotide strand complementary,” “[o]nce the modified nucleotide has been incorporated into the growing polynucleotide chain,” and “successive incorporation of nucleotides into a polynucleotide chain.” EX1043 at 44:62-64, 45:3-5, 45:35-36. These usages show that sequences are “incorporated” as part of a synthesis reaction via sequential addition of nucleotides during the synthesis reaction.

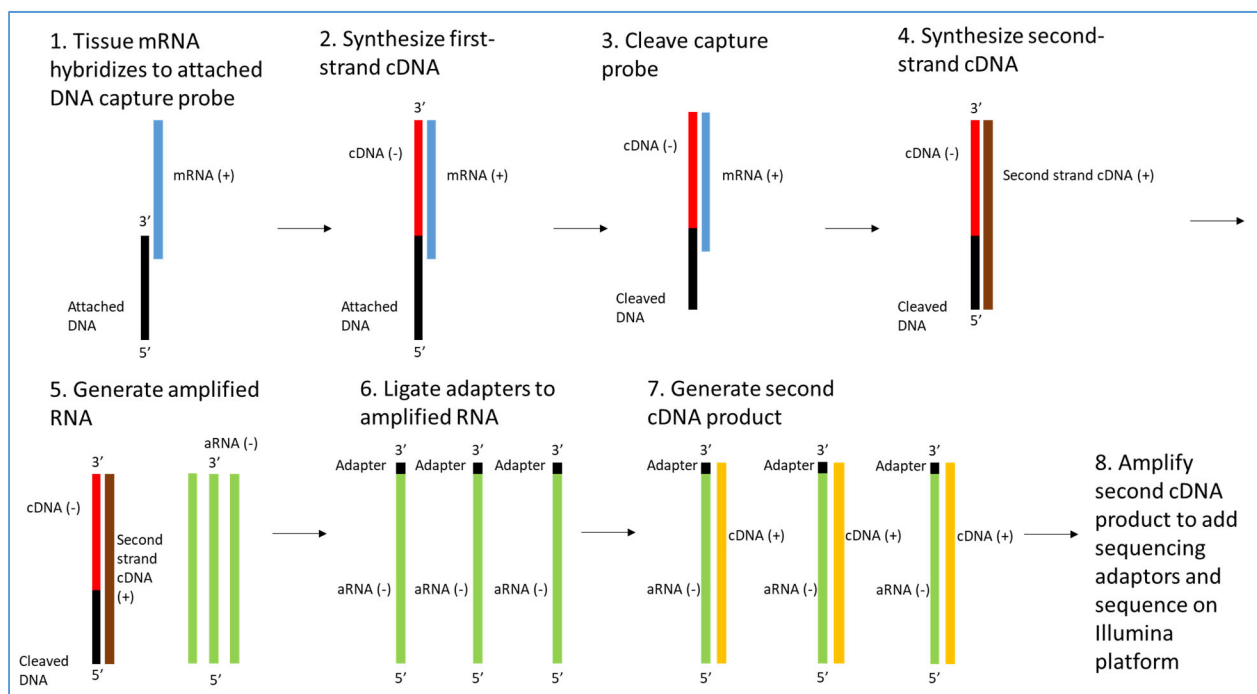
This interpretation is also consistent with embodiments in the specification. EX2008 ¶ 54. Figure 7 is as an example:



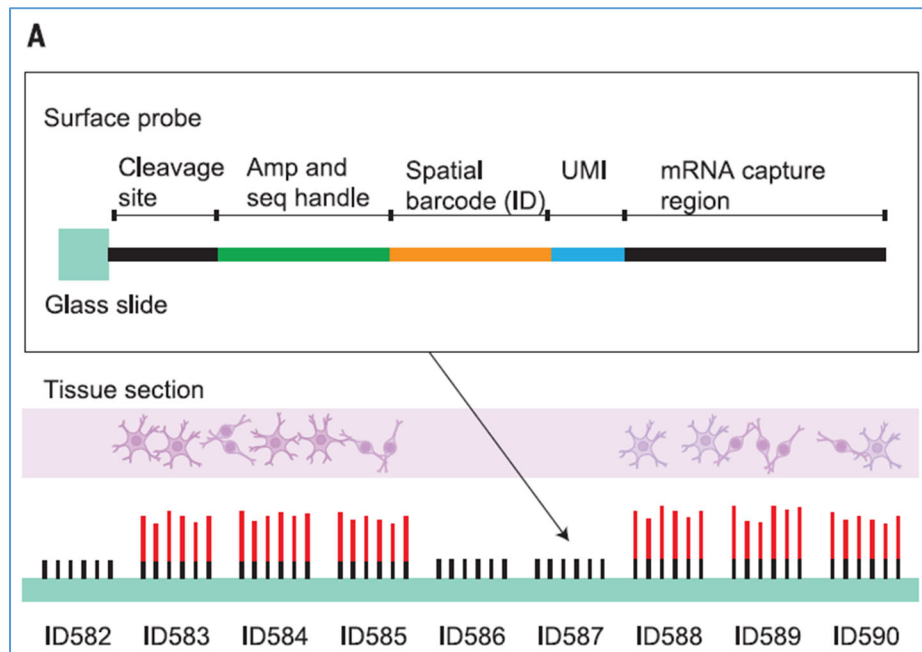
EX1043 Fig. 7. The patent teaches that after an “identifier oligonucleotide” is collected from a region-of-interest of a sample, “a first nucleic acid probe and a second nucleic acid probe” are hybridized to the “identifier oligonucleotide.” *Id.* at 24:17-41. Specifically, the “first or the second nucleic acid probe can also comprise a nucleic acid sequence which identifies the specific location of the sample from which the identifier oligonucleotide was released.” *Id.* at 24:44-47. In Figure 7, the second nucleic acid probe contains the location-identifying sequence. The nucleic acid probes are then ligated, after which the ligation product is

“amplif[ied]...using amplification primers that hybridize to the first and second amplification primer binding site” prior to “sequencing the amplified products.” *Id.* at 26:12-19. Thus, in this example, primers that bind to the “first amplification primer binding site” and the “second amplification primer site” are used to synthesize “DNA products.” Importantly, this synthesis reaction synthesizes the location-identifying sequence.

In Stahl, the first-strand cDNA includes—but does not incorporate—the location-identifying sequence as required by the claim. EX2008 ¶ 55. As depicted by Dr. Sherman’s illustration of Stahl’s workflow, during reverse transcription, the capture probe (depicted in black) is extended to generate cDNA (depicted in red):



Id. ¶ 55. As Stahl specifically illustrates in the figure below, the location-identifying sequence is already present on the capture probe:



EX1016 Fig 2A (depicting “Spatial barcode” in orange). Petitioner does not allege otherwise. *See* Paper 2 at 28 (“Stahl discloses that each capture probe on its array comprises a ‘spatial barcode.’”). Thus, the spatial barcode is not “incorporated” into the synthesized cDNA because the location-identifying sequence is not synthesized.

To the extent Petitioner argues for the first time on reply that the second-strand cDNA in Stahl synthesizes the location-identifying sequence, such an argument would be improper. Petitioner does not identify in its Petition the second-strand cDNA as the claimed “DNA products” or reference the second-strand cDNA in Stahl

for meeting the instant claim element and cannot do so for the first time on reply.

See supra § IV.A.1; Paper 2 at 28-29.

Accordingly, Petitioner fails to show that Stahl anticipates the claims of the '142 patent at least because the location-identifying sequence is not incorporated into the identified “DNA products.”

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

Stahl also does not disclose “amplifying a library using...DNA products,” as required by dependent claim 7. EX2008 ¶¶ 57-65. In addition to the limitations in independent claim 1, claim 7 requires an amplifying step:

7. The method of claim 1, further comprises amplifying a library using the first plurality of DNA products and the second plurality of DNA products as templates.

EX1043 Claim 7. As Dr. Sherman explains, “template” has a plain and ordinary meaning—it is the source of the nucleic acid sequence that is amplified. EX2008 ¶¶ 58-59; EX2015. Petitioner’s expert likewise explains that “the template is the thing being amplified.” EX2009 at 32:16-33:11. Thus, the plain language of claim 7 requires that the “DNA products” must be the template used to amplify a library. EX2008 ¶ 60.

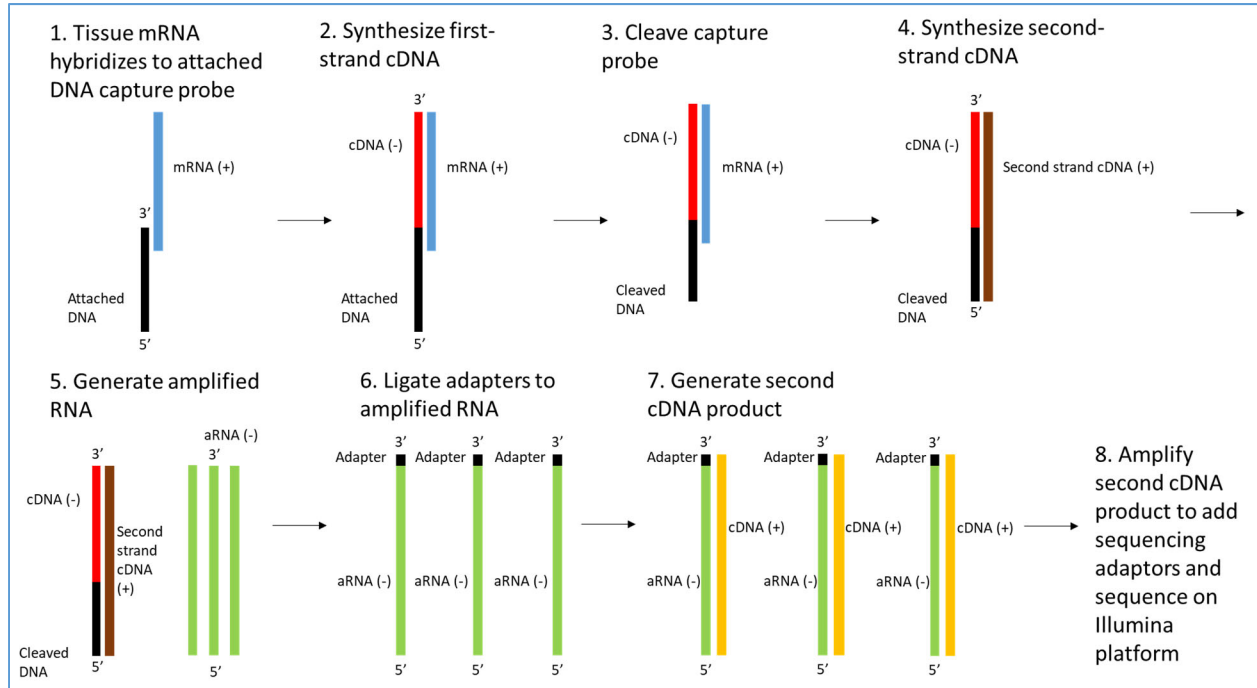
As discussed in Section IV.A.1, Petitioner identifies in Stahl the first-strand cDNA with Cy-3 nucleotides as the “DNA products.” In discussing how Stahl allegedly anticipates claim 7, however, Petitioner confusingly points to two separate amplification steps that do *not* use as templates Petitioner’s identified “DNA products”:

Stahl discloses amplifying “a library” when discussing the workflow for “cDNA library preparation for sequencing.” EX1016, Suppl. Materials, 6-7; EX1044, ¶142. After performing an initial *in vitro* transcription/amplification to produce amplified RNA molecules, Stahl discloses adding DNA adapters to the ends of the amplified RNA, reverse-transcribing the amplified RNA into cDNA, and then performing PCR to *amplify the cDNA* to add Illumina paired-end (PE) sequencing flow-cell binding sites and index sequences before sequencing. EX1016, Suppl. Materials, 7 (“2µl purified cDNA were *amplified by qPCR* ... the samples were *amplified* in a total reaction volume of 25µl.”); EX1044, ¶142.

See Paper 2 at 37 (emphasis and modifications in original). None of the amplification reactions highlighted by Petitioner involve Petitioner’s identified “DNA products” as templates. EX2008 ¶¶ 61-64.

Petitioner’s first and third reference—“performing PCR to *amplify the cDNA* to add Illumina paired-end (PE) sequencing flow-cell binding sites and index sequences before sequencing” and “the samples were *amplified* in a total reaction

volume of 25µl”—both identify the amplification reaction where the second cDNA product (depicted below in orange) is amplified as the template to add sequencing adapters (step 8):



EX2008 ¶¶ 62, 64. The second reference—“2µl purified cDNA were *amplified by qPCR*”—involves amplifying the second cDNA product to “determin[e] the amount of cycles needed based on the qPCR.” EX1016, Suppl. Materials at 7. The product of the qPCR is not sequenced, as required by claim 1(e). *Id.*; EX2008 ¶ 63.

Accordingly, Petitioner fails to additionally show that Stahl anticipates claim 7 of the '142 Patent at least because Petitioner's identified “DNA products” is not used as a template to amplify a library.

B. GROUND 2: CLAIMS 1-13 WOULD NOT HAVE BEEN OBVIOUS OVER STAHL

1. Claims 1-4, 6-13

Petitioner provides no specific contentions that address why the missing elements discussed for Ground 1 would have been obvious. *See* Paper 2 at 44-45; *see supra* § IV.A. For example, Petitioner provides no reason why a POSA would have been motivated to modify Stahl’s method to meet the claimed methods when, as Petitioner contends, “Stahl provides detailed descriptions and protocols” and “the protocol was straightforward.” *Id.* at 45. Thus, Petitioner fails to establish why or how a POSA would modify Stahl’s method to arrive at the ’142 Patent claims. EX2008 ¶¶ 66-70.

2. Claim 5

Claim 5 depends from claim 4 and additionally requires that “each of [Claim 1’s] step (c) and step (d) comprises performing a solid-phase amplification reaction, wherein the solid-phase amplification reaction is carried out on the microscope slide using the plurality of primers immobilized on the microscope slide.” EX1043 Claim 5.

Petitioner does not contend that Stahl discloses this limitation of “performing a solid-phase amplification reaction.” EX2008 ¶ 72. For example, Petitioner concedes that Stahl involves “collecting the first-strand cDNAs and performing

second-strand cDNA synthesis in solution prior to performing library amplification (also in solution).” Paper 2 at 46. Petitioner contends nonetheless that it would have been obvious to modify Stahl’s method because 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.” *Id.* at 47. There is, however, a fundamental difference between the possibility that Stahl’s method ***could have*** been modified compared with whether it ***would have*** been obvious to modify Stahl’s method to add those features. As discussed therein, Petitioner fails to show that a POSA ***would*** have modified Stahl to practice the limitation in claim 5. EX2008 ¶¶ 71-85.

As an initial matter, Petitioner’s proposed modification of the second-strand cDNA synthesis and library amplification fail to meet claim 5 even if they were solid-phase amplifications. *Id.* ¶ 73. Claim 5 requires both claim 1’s steps (c) and (d), which require synthesizing “DNA products,” to include “a solid-phase amplification reaction.” As discussed, neither of these are Petitioner’s identified “DNA products.” *See* Paper 2 at 46 (“As discussed above for claim 1, Stahl’s method performs the synthesis steps (c) and (d) when it synthesizes the cDNA products (***first-strand cDNAs***) on the array.”); *see supra* § IV.A.1. Petitioner does not identify Stahl’s second-strand cDNA or second cDNA product for library

amplification as the claimed “DNA products.” Thus, Petitioner fails to show how Stahl’s synthesis of the first-strand cDNA can be synthesized via “a solid-phase amplification reaction.” Petitioner’s discussion of Stahl’s second-strand cDNA and library amplification has no relevance to claim 5’s limitation because these steps take place *after* the first-strand cDNA is synthesized.

Regardless, a POSA would not have reasonably expected success in modifying Stahl. Petitioner provides no specifics how Stahl can be modified to have a working workflow other than a conclusory statement that “a POSA would have viewed performing second strand synthesis on the substrate as a mere trivial modification.” Paper 2 at 49; EX2008 ¶ 74.

For the second-strand synthesis to take place in solid phase, the release step cleaving the capture probe would have to be skipped. EX2008 ¶ 75. Petitioner’s expert agrees:

Q So if the second-strand cDNA is synthesized on the array, then the step in Stahl where the release mix with a user enzyme is added, that step needs to be skipped. Is that right?

A No, that's --

A It doesn't need to be skipped. Oh, oh, sorry. To do it in -- on the array itself, yes, you would -- you would either -- you would move the order of that potentially, or skip it.

EX2009 at 91:8-20. Removing the cleavage step, however, results only in additional issues. For example, as Dr. Sherman explains, solid-phase reactions are

less efficient than those in solution due to increased mobility and access of the molecules involved, whose movements are restricted in solid phase. EX2008 ¶ 76. In addition, the generation of amplified RNA would be significantly affected if the involved cDNA molecules were in solid phase due to the inaccessibility of the cDNA caused by its proximity to the surface, particularly as the promoter for the involved RNA polymerase is directly adjacent to the surface. *Id.* ¶ 77. Moreover, Petitioner provides no detail on the polymerase to be used for its proposed modifications, which, as Dr. Sherman testifies, greatly differ between solid-phase and solution-phase amplification. *Id.* ¶ 74. Petitioner's contention that "library amplification can be performed on Stahl's array," Paper 2 at 47, is likewise without merit. Stahl's workflow involves the generation of amplified RNA, which offers the advantage of strand preservation, a function integral to Stahl. EX2008 ¶ 78; EX2011 at 174; EX2012 at 1. Replacing the generation of amplified RNA with clonal amplification where the amplification occurs on the surface would necessitate a number of modifications including appending adapters to the cDNA and attaching complementary primers to the surface. EX2008 ¶ 78. The successful implementation of such modification is unlikely due to the amount of experimentation required and unwarranted due to the loss of strand preservation. *Id.* Without strand preservation, the modified workflow would result in a loss of

specificity and less accurate quantitative gene expression data, one of the objectives of Stahl's method. *Id.*

In addition to the low likelihood of success, a POSA would not have been motivated to modify Stahl. EX2008 ¶¶ 79-84. While Petitioner contends that "Stahl in view of the POSA's general knowledge in the art suggests performing claim 5's solid-phase amplification reaction," Paper 2 at 47, such reasoning goes against common sense. *Id.* ¶ 79. In addition to the reasons stated in Section IV.C, Frisen was filed in 2011 and published in 2012, years before Stahl's publication in 2016. Thus, Stahl's inclusion of a step to release the first-strand cDNA from the array is deliberate because, as Petitioner contends, Stahl's authors knew how to perform workflows in Frisen. Rather than modify Stahl's method using Frisen, a POSA would expect the authors of Stahl to publish an optimal method within their knowledge that works. As Petitioner's expert explains, Stahl's authors "found something that worked" despite being fully aware of solid-phase amplification. EX2009 at 100:3-101:10.

Furthermore, even Stahl's authors, who Petitioner credits with creating spatial array barcoding, commercialized their method which, even in 2023, was performed *without* solid-phase second-strand cDNA synthesis. *See* EX1018 at 7

(“The cDNA-RNA-hybrids are cleaved off the chip.”); EX2008 ¶ 80. Thus, Frisen does not suggest modifying Stahl.

Petitioner also contends that “solid-phase amplification ‘significantly minimizes undesirable primer interactions.” Paper 2 at 48. As Dr. Sherman explains, this is not a concern with Stahl because the same primers in Stahl are used for amplification—there are no different species of primers that can potentially form primer dimers. EX2008 ¶ 81. Similarly, the alleged benefits of “sensitivity and selectivity” touted by Petitioner is uncertain, as even Petitioner’s cited reference states that “the emergence of ‘active’ arrays *may* provide the sensitivity and selectivity for nucleic acid identification and genotyping,” as “it is quite clear that the technology is being pushed towards to a microbead-based platform,” unlike the slide-bound reactions proposed by Petitioner. EX1048 at 11; EX2008 ¶ 82.

In addition, a POSA would have been concerned with the numerous then-known drawbacks of solid-phase amplification. EX2008 ¶ 83. For example, problems unique to solid-phase amplification such as electrostatic forces, the finite number of primers, polymerase and nucleotide availability, sterile molecules, and DNA stiffness can all affect the reaction. EX2013 at 40-41. Moreover, steric hindrance is a dominating effect that limits solid-phase amplification. *Id.* at 32. Even a reference cited by Petitioner highlights that solid-phase amplification is

subject to issues such as “a molecule at the center of the colony (which is surrounded by others) will have a smaller duplication probability (its free end is less likely to find a matching primer on the surface,” “a sterile molecule [] occupies space [and] applies steric constraints to its neighbors and can prevent them from duplicating,” “a primer (or an attached molecule)...[can] break away from the surface,” and “it is very difficult for a molecule surrounded by others to bend so that its end can find a matching primer.” EX1050 at 2079, 2081, 2083-2084. In light of these issues, a POSA would not have been motivated to modify Stahl with solid-phase amplification. EX2008 ¶ 83.

A POSA would also have recognized that Stahl’s first-strand cDNA synthesis is a solid-phase reaction. As Dr. Sherman explains, any of the benefits cited by Petitioner as a result of performing a reaction in solid-phase is already accrued by the first-strand cDNA synthesis. EX2008 ¶ 84. Modifying Stahl so that additional reactions are solid-phase would lead only to a decrease in reaction efficiency in addition to encountering the issues discussed. *Id.*

Accordingly, a POSA would have had no reason to modify Stahl’s method other than to meet claim 5’s limitation and no reason to expect any modification to succeed. As such, Petitioner fails to show that claim 5 would have been obvious over Stahl.

**C. GROUND 3: CLAIM 5 WOULD NOT HAVE BEEN OBVIOUS
OVER STAHL AND FRISEN**

Petitioner rehashes much of its argument from Ground 2 that a POSA would have modified Stahl’s method. EX2008 ¶¶ 86-95. The same arguments and evidence set forth above with respect to Ground 2 apply equally here. *See supra* § IV.B.2; EX2008 ¶ 86.

Petitioner contend that Frisen discloses “using solid-phase second-strand cDNA synthesis and solid-phase library amplification steps, both of which are ‘solid-phase amplification.’” Paper 2 at 51. As explained above, neither second-strand cDNA synthesis nor library amplification steps are part of the synthesis reaction to synthesize DNA products, as required by the claims. EX2008 ¶ 87.

In addition, while Frisen suggests that synthesis of the second-strand cDNA and amplification of the double-stranded cDNA can occur in solid phase, it also makes clear that these are *optional*. *See* EX1017 Abstract (“The present invention...comprises...(d) *optionally* generating a complementary strand of said tagged DNA and/or *optionally* amplifying said tagged DNA....”); EX2008 ¶ 88. Frisen explains two ways this optional step may take place. The second-strand cDNA synthesis “may be achieved by any means known in the art...whilst the cDNA is immobilized on the array, or preferably after the cDNA has been released from the array substrate.” EX1017 at 39:3-7. Or, “the first strand of the secured

nucleic acid, e.g. cDNA molecules, which comprise also the capture probe of the features of the array, acts as a template for the amplification reaction, e.g. a polymerase chain reaction.” *Id.* at 39:11-14. “The first reaction product of the amplification will be a second strand of DNA, e.g. cDNA, which itself will act as a template for further cycles of the amplification reaction.” *Id.* at 39:14-17. As Dr. Sherman explains, a POSA would not modify Stahl based on Frisen because Frisen does not disclose strand preservation, required by Stahl, or clonal amplification, required for Petitioner’s proposed modification. EX2008 ¶¶ 89-90.

Nonetheless, a POSA would not be motivated to modify Stahl with either of these optional steps from Frisen. First, while Petitioner touts Frisen to disclose “applications and modifications of Stahl’s spatial barcoding array workflow,” Paper 2 at 53, a POSA would not have understood this to be the case as Stahl’s publication date in 2016 *post-dates* Frisen’s filing and publication date by years. EX2008 ¶ 91.

Second, while Petitioner contends that “solid-phase second-strand cDNA synthesis and/or solid-phase library amplification offers certain advantages,” *id.*, Stahl’s method already benefits from solid-phase first-strand cDNA synthesis, as discussed. *See supra* § IV.B.2; EX2008 ¶ 92. Frisen’s optional step does not involve clonal amplification. *Id.* ¶ 93. Without clonal amplification, Petitioner’s proposed modification of Stahl’s method with Frisen would not benefit from reduced

“undesirable primer interactions,” Paper 2 at 54, because the primers would still be in solution, or “parallelization of the DNA amplification process,” *id.*, because Stahl’s workflow already includes location-identifying sequences to allow determination of the location of the captured mRNA after amplifying multiple targets. *See* EX2008 ¶¶ 93-94.

Third, Frisen’s optional steps provide no advantages over Stahl’s unmodified method and lead to disadvantages in efficiency and yield in performing additional steps in solid phase, as discussed. *Id.* ¶ 94; *see supra* § IV.B.2.

Fourth, to the extent Petitioner contends that clonal amplification can be implemented, Petitioner offers no reason to replace Stahl’s existing amplification steps, as discussed. EX2008 ¶ 94; *see supra* § IV.B.2.

A POSA would also not expect modifying Stahl with Frisen’s optional steps to succeed. EX2008 ¶ 95. Petitioner simply does not provide sufficient specifics on *how* Stahl can be easily modified with Frisen. As discussed, amplified RNA cannot readily be generated from the first-strand/second-strand cDNA if it is attached to solid support. *See id.* Also, to the extent Stahl is modified to implement clonal amplification, significant changes would have to be made, from which Frisen provides minimal details. *See id.*

Accordingly, claim 5 would not have been obvious over Stahl in view of Frisen.

D. GROUND 4: SO-456 DOES NOT ANTICIPATE CLAIMS 1-13

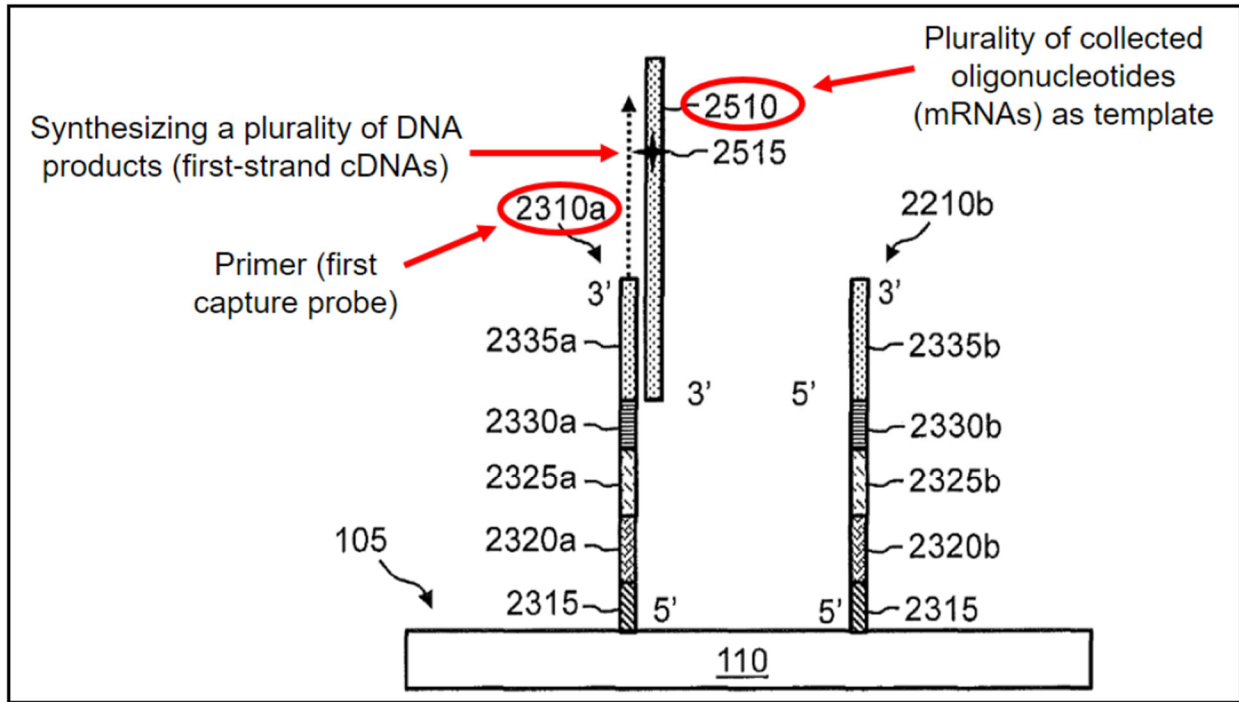
Petitioner contends that So-456 anticipates all claims of the '142 Patent. So-456, however, does not anticipate all claims of the '142 Patent. EX2008 ¶ 96.

1. So-456 Does Not Incorporate A Nucleic Acid Sequence That Identifies Location

As discussed, claim 1(c) and 1(d) requires synthesizing “DNA products” that incorporate a spatial barcode:

synthesizing a [first]/[second] plurality of DNA products by performing a synthesis reaction that uses the plurality of oligonucleotides collected in step [(a)/(b)] as templates and incorporates at least one nucleic acid sequence that identifies the [first/second] location of the tissue sample into each of the [first/second] plurality of DNA products;

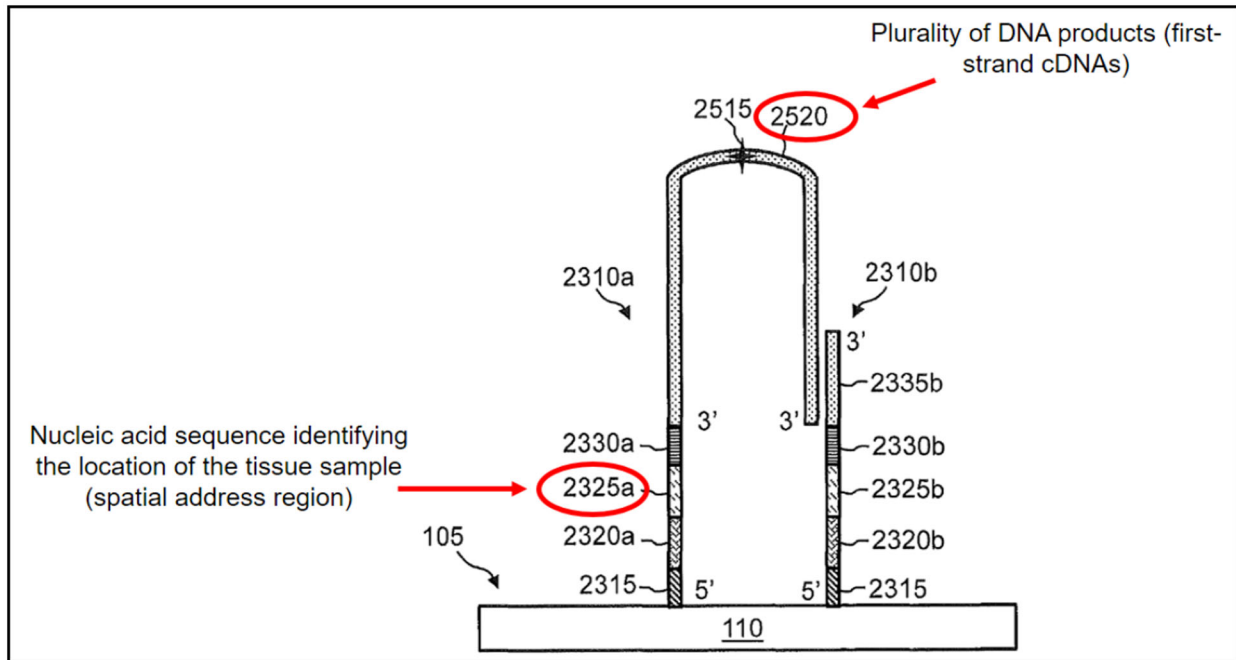
EX1043 Claim 1(c), 1(d). For So-456, Petitioner identifies the first-strand cDNA as the claimed “DNA products”: “So-456’s method uses the ‘gene-specific capture regions on the first capture probe’ (2310a) as ‘reverse transcriptase primers’ for ‘synthesis of first strand cDNA from captured mRNA molecules.’” Paper 2 at 61. EX2008 ¶¶ 97-98. In particular, Petitioner includes an annotated figure to illustrate synthesis of the first-strand cDNA identified as “DNA products”:



Id.; EX2008 ¶ 99.⁴

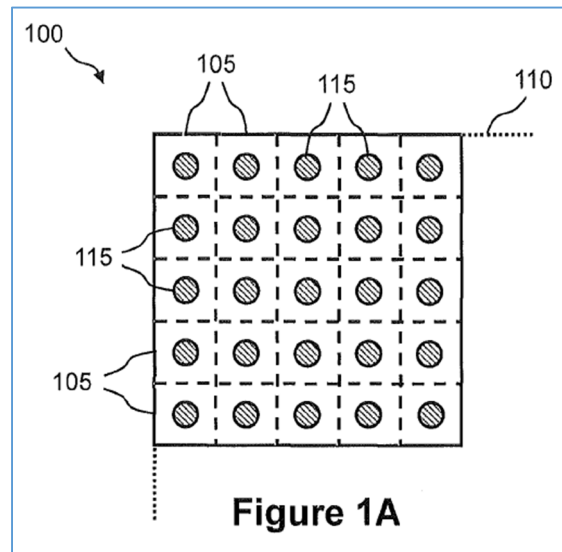
Petitioner contends that the first-strand cDNA incorporates a spatial barcode due to spatial address region 2325a on the capture probe, as shown in another annotated figure from Petitioner:

⁴ See *supra* fn.2. Petitioner specifically identified the first-strand cDNA as the claimed “DNA products.”



Id. at 64; EX2008 ¶ 100.

As is clear from Petitioner's figure, however, only half of the sequence necessary to determine location is part of the cDNA strand—spatial address region 2325a, but not 2325b—is part of the first-strand cDNA. As So-456 makes clear, the encoding scheme is an X-Y arrangement of capture sites, such that rows and columns are necessary to determine the location:



EX1005 Fig. 1A; *id.* ¶ 141. In the specific embodiment identified by Petitioner, So-456 further explains that sequence 2325a is a “unique spatial address for the X dimension” and 2325b is a “unique spatial address for the Y dimension.” *Id.* ¶ 318. Accordingly, in order to determine the location of the sample, sequences denoting both the X-dimension (2325a) and Y-dimension (2325b) are required. EX2008 ¶ 99.

Since sequence 2325b is not part of the first-strand cDNA, which Petitioner identifies as the “DNA products,” Petitioner fails to show that So-456 discloses synthesizing “DNA products” that incorporate “at least one nucleic acid sequence that identifies the [] location of the tissue sample,” as required by claim 1. The first-strand cDNA includes only sequence 2325a, or information on the X

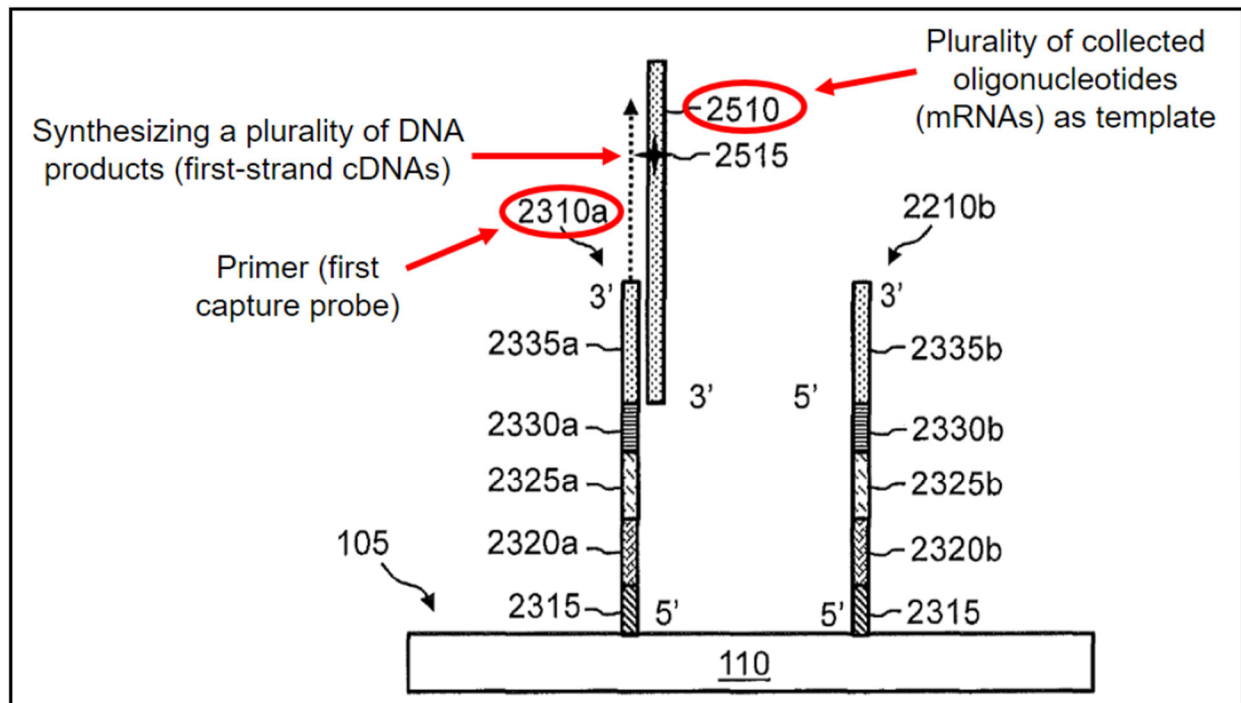
dimension. That is insufficient to determine a location of the tissue sample.
EX2008 ¶ 101.

For at least this reason, So-456 does not anticipate the '142 Patent claims.
EX2008 ¶ 102.

2. So-456 Does Not Disclose A Synthesis Reaction That Incorporates A Nucleic Acid Sequence That Identifies Location

As discussed for Stahl, claims 1(c) and 1(d) require “incorporating” a spatial barcode (“a nucleic acid sequence that identifies the [] location of the tissue sample”) during the synthesis of “DNA products.” § IV.A.2. This “incorporate” claim element requires synthesizing a spatial barcode. *Id.*; EX2008 ¶ 103-104.

The situation with So-456 is similar to that with Stahl. The first-strand cDNA in So-456, which Petitioner identifies as “DNA products,” includes but does not “incorporate” by synthesis the spatial address region (which, as explained in the prior section, is insufficient to identify a location of a tissue sample). As depicted in Petitioner’s annotated figure, synthesis of the first-strand cDNA involves extending the capture probe, which already contains the spatial address region
2325a:



Paper 2 at 61. Thus, the spatial address region 2325a is not “incorporated” into the generated cDNA, Petitioner’s identified “DNA products,” because the spatial address region is not synthesized. EX2008 ¶ 105.

Accordingly, Petitioner also fails to show that So-456 anticipates the claims of the ’142 Patent at least because Petitioner’s identified spatial address region (2325a) is not “incorporated” into the “DNA products.” EX2008 ¶ 106.

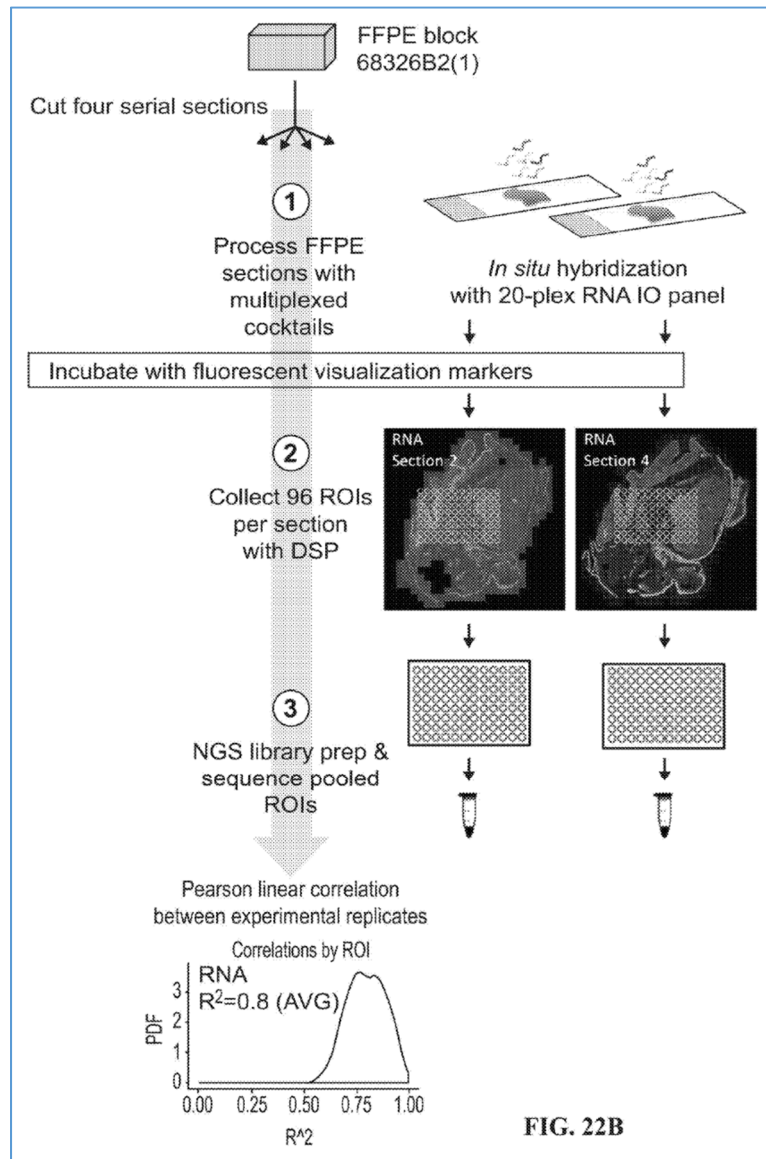
3. So-456 Does Not Disclose Condition That Release Oligonucleotides

Claims 1(a) and 1(b) require a “collecting a plurality of oligonucleotides from a [first]/[second] location of a tissue sample *under conditions that release the*

plurality of oligonucleotides from the [first]/[second] location of the tissue.”

EX1043 Claim 1; EX2008 ¶¶ 107-108.

As Dr. Sherman explains, a POSA would have recognized the importance of treating a tissue sample so that nucleic acids can be released from the sample for subsequent collection. EX2008 ¶ 109. The '142 patent, for example, teaches such a treatment as part of a workflow:



EX1043 Fig. 22B. As the figure depicts, a FFPE block is sectioned and processed with “multiplexed cocktails” before incubation and further analysis. *Id.* Processing of the FFPE sample provides a specific condition that allows mRNA to be released and collected. As Dr. Sherman explains, it would be impossible to analyze a tissue sample, wherein the sample nucleic acids are fixed and otherwise

unavailable for analysis, without first treating the sample so that the sample nucleic acids are released, such as a permeabilization or lysing step. EX2008 ¶ 110. For example, for Stahl, Petitioner identifies a permeabilization step where “the tissue sample was treated with ‘0.01% pepsin ... dissolved in 0.1M HCl,’ to release the mRNAs from the tissue.” Paper 2 at 26; EX2008 ¶ 111.

In contrast, Petitioner fails to identify any disclosure by So-456 of treating a tissue sample such that it is under conditions that release the oligonucleotides in the tissue sample. For example, Petitioner cites a number of paragraphs that are nothing more than sectioning the tissue and placing it on a capture array:

- “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.” EX1005 ¶ 152.
- “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.” *Id.* ¶ 154.
- “At a step 2410, a tissue sample that comprises a plurality of mRNA molecules is contacted with a capture array.” *Id.* ¶ 308.

- “For example, the tissue sample containing mRNA molecule 2510 or a substrate comprising mRNA molecule 2510 derived from the tissue sample (not shown) is contacted with capture probes 2310.” *Id.* ¶ 315.

A POSA would not have understood these disclosures to place the tissue “under conditions that release” sample mRNA. EX2008 ¶¶ 112-113.

Petitioner additionally contends that “the tissue sample was treated to create a condition to ‘release’ the mRNA from the tissue onto the array” because So-456 describes steps that involve the mRNA. Paper 2 at 60-61. Such reasoning is conclusory at best. Petitioner’s contention that the tissue sample must somehow have been treated does not equate to a disclosure by So-456 of such treatment to meet the high bar of anticipation. EX2008 ¶ 114.

Petitioner’s argument that So-456 must have disclosed “conditions that release the plurality of oligonucleotides” from a tissue sample is an unstated and misguided inherency argument. For example, Petitioner’s expert agreed that this claim element “necessarily must be present in So-456” because So-456 “says the array elements collect the mRNA.” EX2009 at 119:13-21; *see PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must, therefore, meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis—the limitation at

issue *necessarily must be present*, or the natural result of the combination of elements explicitly disclosed by the prior art.”). Petitioner should be foreclosed from making an inherency argument since inherency was not invoked in the petition. EX2008 ¶ 115.

Accordingly, So-456 does not anticipate ’142 Patent claims 1-13 additionally because So-456 does not disclose treating a tissue sample so that oligonucleotides are released. EX2008 ¶ 116.

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

As discussed, claim 5 requires that “each of [Claim 1’s] step (c) and step (d) comprises performing a solid-phase amplification reaction, wherein the solid-phase amplification reaction is carried out on the microscope slide using the plurality of primers immobilized on the microscope slide.” EX1043 Claim 5; § IV.B.2; EX2008 ¶¶ 117-118.

Here, Petitioner identifies So-456’s first-strand cDNA as the claimed “DNA products.” § IV.D.1. Thus, Petitioner must show how synthesis of the first-strand cDNA is performed in So-456 using a solid-phase amplification reaction. Instead, Petitioner identifies So-456’s second-strand cDNA synthesis for allegedly being performed using a solid-phase amplification reaction. Paper 2 at 69-71. As the second-strand cDNA is not Petitioner’s identified “DNA products,” synthesis of the

second-strand cDNA takes place *after* synthesis of the first-strand cDNA, Petitioner's identified "DNA products." EX2008 ¶ 119.

Accordingly, Petitioner fails to show that claim 5's limitation are met during synthesis of Petitioner's identified "DNA products."

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

As discussed, claim 7 requires "amplifying a library using...DNA products as templates." EX1043 Claim 7; § IV.A.3. In order to meet this claim, Petitioner has the burden to show that its identified "DNA products" are used as templates in an amplification reaction. *See id.*; EX2008 ¶ 120.

Petitioner, however, shows that the second-strand cDNA in So-456 is what is used as a template in an amplification reaction and not the first-strand cDNA, Petitioner's identified "DNA products." While Petitioner states that the second-strand cDNA is synthesized "using the first-strand cDNA as templates," Paper 2 at 72, Petitioner nonetheless states that "the second strand cDNAs (2525) are released from the array and 'amplified to generate a sequencing library.'" *Id.* Thus, Petitioner concedes that the second-strand cDNA is what is "amplified to generate a sequencing library." As Dr. Sherman explains, a POSA would have understood the actual molecule being amplified, the second-strand cDNA, to be the template in the amplification reaction. EX2008 ¶ 121.

So-456 corroborates this understanding. So-456 first discloses that “second strand cDNA is synthesized in an extension reaction using capture region 2335b as a primer.” EX1005 ¶ 318. Then, “a cDNA molecule 2525 is released from capture site 105 by cleavage of cleavable region 2315.” *Id.* ¶ 319. Finally, “cDNA molecule 2525 is amplified using an SBS primer 2530 and a second SBS primer 2535.” *Id.* ¶ 320; EX2008 ¶¶ 122.

The first-strand cDNA, Petitioner’s identified “DNA products,” is different from the second-strand cDNA. In addition to these being two different strands and having part of their sequence being inversely complementary, the second-strand cDNA also includes additional sequences that are not part of the first-strand cDNA. For example, So-456 notes that “SBS primer 2535 comprises an SBS region 2320b’ that is complementary to SBS primer region 2320b.” *Id.* Primer region 2320b, however, is part of the second-strand cDNA but *not* the first-strand cDNA, Petitioner’s identified “DNA products.” Thus, the amplification primers used to amplify the second-strand cDNA would not function to amplify the first-strand cDNA. EX2008 ¶ 123.

Accordingly, Petitioner fails to show that So-456 anticipates claim 7 because Petitioner’s identified “DNA products” is not used as a template and amplified to generate a sequencing library.

E. GROUND 5: CLAIMS 1-13 WOULD NOT HAVE BEEN OBVIOUS OVER SO-456

Petitioner provides no specific contentions that address why the missing elements discussed for Ground 4 would have been obvious. *See* Paper 2 at 77-79; EX2008 ¶¶ 124-125.

Petitioner argues that a “POSA reading So-456 would have been motivated to practice the claimed methods because, e.g., So-456 teaches a ‘method ... of spatial detection and analysis of a nucleic acid (i.e., at least one target analyte) in a tissue sample’ using spatially barcoded arrays.” Paper 2 at 78. This, however, shows only that So-456 and the ’142 Patent are directed to similar fields of endeavor. Without specific reasons, such as an advantage or benefit, a POSA would not have been motivated to modify So-456 to arrive at the claimed invention. EX2008 ¶ 126.

Accordingly, as Petitioner provided no specific modifications of So-456, the ’142 Patent would not have been obvious over So-456 due to the missing claim elements discussed in Ground 4.

V. CONCLUSION

For the reasons set forth above, 10x’s Petition for *Inter Partes* Review should be denied in its entirety.

Dated: November 20, 2024

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 11,122 words as calculated by the “Word Count” feature of Microsoft Word 2016, the word processing program used to create it.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: November 20, 2024

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PATENT OWNER'S RESPONSE TO PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 11,473,142 and EXHIBITS 2007-2017** were served on November 20, 2024, via email pursuant to 37 C.F.R. § 42.6(e) to counsel for Petitioner at the addresses below:

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