

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.,
Petitioner,

v.

BRUKER SPATIAL BIOLOGY, INC.,
Patent Owner.

IPR2023-01300
Patent 11,473,142 B2

Before SUSAN L. C. MITCHELL, DEVON ZASTROW NEWMAN, and
JAMIE T. WISZ, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314, 37 C.F.R. § 42.4

I. INTRODUCTION

A. *Background and Summary*

Petitioner, 10X Genomics, Inc., (“Petitioner”) filed a Petitioner for *inter partes* review of claims 1–13 of U.S. Patent No. 11, 473,142 (“the ’142

patent”). Paper 2 (“Pet.”). Then-Patent Owner NanoString Technologies, Inc., (“NanoString”) filed a Preliminary Response (Paper 6 “Prelim. Resp.”). With our authorization (Ex. 3001), Petitioner filed Petitioner’s Pre-Institution Reply (Paper 7, “Pet. PI Reply”). Before NanoString’s deadline for filing its sur-reply, NanoString instead filed a petition for relief under chapter 11 of the Bankruptcy Code in the United States Bankruptcy Court for the District of Delaware, and all deadlines in this proceeding were stayed pending notification that the Bankruptcy Court had lifted the stay with respect to this proceeding. Paper 15.

On July 15, 2024, Bruker Spatial Biology, Inc., filed an Unopposed Motion to Substitute Party, seeking to substitute itself as Patent Owner, and explaining that the bankruptcy court approved an agreed order to sell certain of NanoString’s property, including the patent challenged in this proceeding, U.S. Patent No. 11, 473,142, to Bruker Corporation, which subsequently assigned its rights and obligations in the patent to Bruker Spatial Biology, Inc. Paper 18; Ex. 3004 (referencing proceeding at issue regarding the ’142 patent). The acquisition closed on May 6, 2024. *Id.* Bruker Spatial Biology, Inc. (“Patent Owner”), also filed updated mandatory notices identifying itself as the Patent Owner and real party in interest in this proceeding. Paper 19. We granted Patent Owner’s Motion to Substitute Party on July 30, 2024. Paper 21. Patent Owner also filed Patent Owner’s Pre-Institution Sur-reply (Paper 17, “PO PI Sur-reply”).

We have jurisdiction under 35 U.S.C. § 314. Under § 314, an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). The Board

determines whether to institute a trial on behalf of the Director. 37 C.F.R. § 42.4(a). A decision to institute is “a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition.” *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018).

For the reasons set forth below, we determine that Petitioner has demonstrated that there is a reasonable likelihood that at least one of the challenged claims is unpatentable. Accordingly, we institute an *inter partes* review of the challenged claims in the Petition.

B. Real Parties-in-Interest

Petitioner identifies itself as the real party-in-interest. Pet. 80. Patent Owner identifies Bruker Spatial Biology, Inc., Bruker Nano, Inc., and Bruker Corporation as the real parties-in-interest. Paper 19, 1 (Patent Owner’s Updated Mandatory Notice).

C. Related Matters

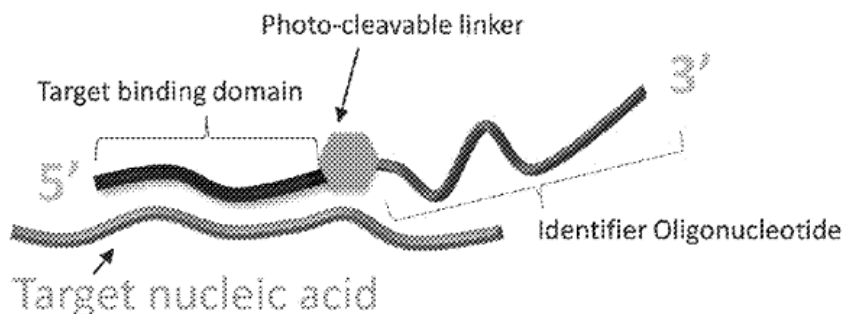
Petitioner identifies a related litigation in which the ’142 patent was asserted, *NanoString Technologies, Inc. v. 10x Genomics, Inc.*, Case No. 1:22-cv-01375 (D. Del.). Petitioner also identifies a related litigation in which sibling U.S. Patent No. 11,377,689 is at issue, *10x Genomics, Inc. and President and Fellows of Harvard College v. NanoString Technologies, Inc.*, Case No. 1:22-cv-00261 (D. Del.). Pet. 81. Petitioner also identifies a related matter before us, IPR2023-01298, in which we instituted an *inter partes* review of claims 1–30 of related U.S. Patent 11,377,689 B2.

Patent Owner identifies *Bruker Spatial Biology Inc., et al. v. 10x Genomics, Inc.*, Case No. 1:22-cv-01375 (D. Del.) as a related litigation. Paper 19, 2.

D. The '142 Patent

The '142 patent issued on October 18, 2022, from U.S. Appl. No. 17/476,712 (“712 application”), filed September 16, 2021. Ex. 1043, codes (45), (21) (22). The 712 application is a continuation of 16/272,487 (“487 application”; Ex. 1009), filed on February 11, 2019, which claims priority to U.S. Appl. Nos. 62/771,212, filed November 26, 2018, and 62/629,180 (Ex. 1043), filed February 12, 2018. *Id.*, codes (63), (60).

The '142 patent is directed to methods for spatially detecting nucleic acids in a tissue sample. Ex. 1043, 1:44–67. The method uses nucleic acid probes to bind to target nucleic acids (“analytes”) within the tissue sample that contain two segments and a linker, as shown below in an excerpt reproduced below from Figure 12:



Reproduced above is an excerpt of Figure 12 of the patent, showing an oligonucleotide probe having three components: 1) a target binding domain, 2) a cleavable linker; and 3) an identifier oligonucleotide. *Id.*, Figure 12. The target binding domain is “is a region of the probe that specifically binds to at least one target analyte in a sample.” *Id.* at 37:23–25. Multiple locations may be probed within the tissue sample using different nucleic acid probes. *Id.* at 33:33–49. The cleavable linker joins the two nucleotide regions in the primer and “allows release of an identifier oligonucleotide from a bound target nucleic acid or protein and the identifier oligonucleotide

can then be collected and detected.” *Id.* at 39:23–25. In one embodiment, the linker permits release of the identifier oligonucleotide when exposed to a sufficient wavelength of light. *Id.* at 17:4–9.

The identifier oligonucleotide is “a nucleic acid molecule that identifies the target analyte bound to the target binding domain. [It] comprises a unique nucleic acid sequence that identifies the target analyte bound to the target binding domain of the probe.” *Id.* at 38:36–40.

Figure 20, reproduced below, is a schematic overview of the methods of the ’142 patent.

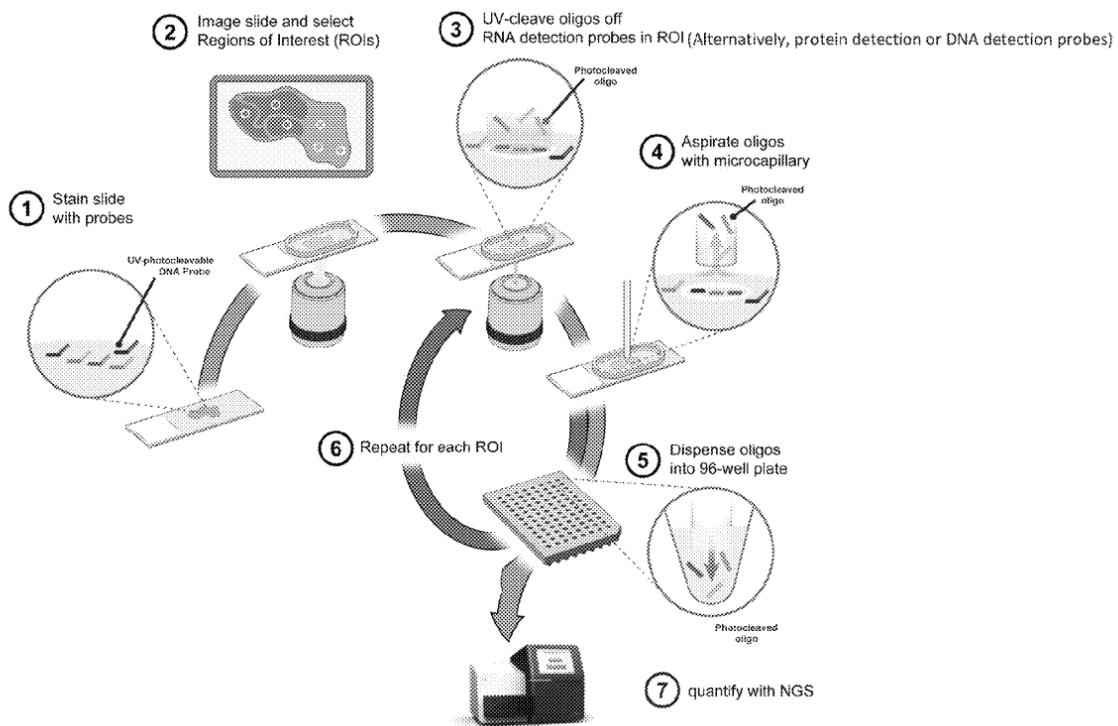


FIG. 20 is an exemplary schematic of overview of the methods of the present disclosure. First, a sample on a microscope slide is contacted with a plurality of probes of the present disclosure (step 1 in FIG. 20). The slide is then imaged and particular regions of interest (ROIs) are selected (step 2 in FIG. 20). A specific ROI is then illuminated by UV light to release identifier oligonucleotides from probes bound within the

ROI. The released identifier oligonucleotides are then collected via aspiration with a microcapillary. Following aspiration, the identifier oligonucleotides are transferred to a particular well within a 96 well plate. Steps 4 and 5 are then repeated for each ROI identified in step 2. After all ROIs have been illuminated and all released identifier oligonucleotides collected, the identifier oligonucleotides are sequenced using next generation sequencing methods to spatially detect at least one target analyte in the sample.

Id. at 36:62–37:18.

In “a preferred aspect of a direct PCR method of the present disclosure,” after cleavage of the linker, the identifier oligonucleotide is amplified in a manner that facilitates identification of the location of the sample to which the oligonucleotide was bound. *Id.* at 32:57–58. Figure 11, reproduced below, depicts an embodiment in which the identifier nucleotide is amplified, including the portion comprising the unique molecular identifier.

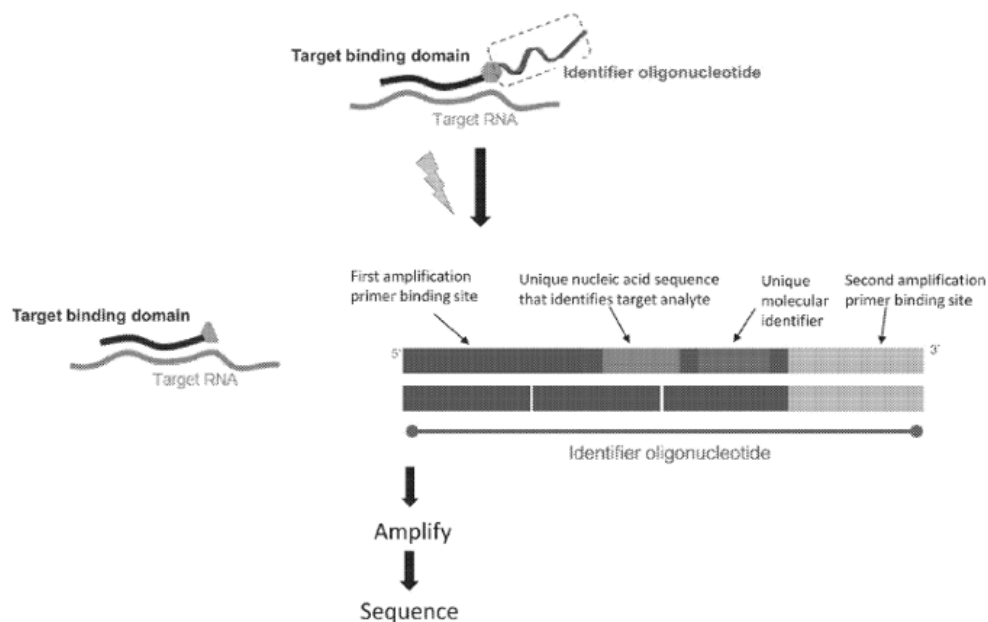


Figure 11 “shows a schematic of a preferred aspect of a direct PCR method” of the ’142 patent. *Id.* at 32:27–51. After the probe hybridizes and the

identifier nucleotide is cleaved, amplification of the identifier oligonucleotide occurs, which is initiated by binding of amplification primers at the first and second binding sites at the borders of the identifier oligonucleotide. *Id.* “The amplified product is then sequenced to identify the target nucleic acid bound by the probe.” *Id.* at 32:55–56. The ’142 patent refers to this process as “spatially detecting” a target analyte. *See, e.g., id.* at 30:51–31:5.

The claimed method relates to collecting oligonucleotides from a first and second location of a tissue sample, “synthesizing” a first and second plurality of DNA products that incorporates one or more nucleic acid sequences that identify the tissue sample locations, followed by sequencing the DNA products to spatially detect the collected oligonucleotides. *Id.*, 147:33–148:62.

E. Illustrative Claims

Claim 1 is the sole independent claim, and is reproduced below as representative of the challenged claims:

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.

Ex. 1043, 147:33–61.

The remaining claims depend from claim 1 and specify components used in the method or the practice of the method steps themselves (e.g., simultaneous performance of specific recited steps). *Id.* at 147:62–148:62.

F. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–13 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. § ¹	Reference(s)/Basis
1	1–4, 6–13	102	Stahl ²

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the ’142 patent claims priority to a provisional application filed after the effective date of these AIA amendments, we apply the AIA version of 35 U.S.C. § 102 and § 103.

² Stahl et al., *Visualization and analysis of gene expression in*

Ground	Claim(s) Challenged	35 U.S.C. § ¹	Reference(s)/Basis
2	1–13	103	Stahl
3	5	103	Stahl, Frisen ³
4	1–13	102	So-456 ⁴
5	1–13	103	So-456

In support of its contentions, Petitioner relies on the Declaration of Paul T. Spellman, Ph.D. (Ex. 1044).

II. ANALYSIS

A. Legal Standards

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)).

“A claim is anticipated [under 35 U.S.C. § 102] only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Moreover, “[b]ecause the hallmark of anticipation is prior invention, the prior art reference—in order to

tissue sections by spatial transcriptomics, SCIENCE 353(6294):78–82, July 1, 2016 (Ex. 1016, “Stahl”).

³ WO 2012/140224 A1, published October 18, 2012 (Ex. 1017, “Frisen”).

⁴ WO 2017/019456 A2, published February 2, 2017 (Ex. 1005, “So-456”).

anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements ‘arranged as in the claim.’” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). Whether a reference anticipates is assessed from the perspective of an ordinarily skilled artisan. *See Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003).

Section 103(a) forbids issuance of a patent when “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) when available, evidence such as commercial success, long felt but unsolved needs, and failure of others. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *see KSR*, 550 U.S. at 407 (“While the sequence of these questions might be reordered in any particular case, the [*Graham*] factors continue to define the inquiry that controls.”). The Court in *Graham* explained that these factual inquiries promote “uniformity and definiteness,” for “[w]hat is obvious is not a question upon which there is likely to be uniformity of thought in every given factual context.” 383 U.S. at 18.

The Supreme Court made clear that we apply “an expansive and flexible approach” to the question of obviousness. *KSR*, 550 U.S. at 415.

Whether a patent claiming the combination of prior art elements would have been obvious is determined by “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.* at 417. To support this conclusion, however, it is not enough to show merely that the prior art includes separate references covering each separate limitation in a challenged claim. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). Rather, obviousness additionally requires that a person of ordinary skill at the time of the invention “would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.” *Id.*; *see also Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1273 (Fed. Cir. 2018) (“The question is not whether the various references separately taught components of the ’330 Patent formulation, but whether the prior art suggested the selection and combination achieved by the ’330 inventors.”).

“In determining whether there would have been a motivation to combine prior art references to arrive at the claimed invention, it is insufficient to simply conclude the combination would have been obvious without identifying any reason why a person of skill in the art would have made the combination.” *Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358, 1366 (Fed. Cir. 2017) (emphasis added). As a factfinder, we also must be aware “of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.” *KSR*, 550 U.S. at 421.

Applying these general principles, we consider the evidence and arguments of the parties.

B. Level of Ordinary Skill in the Art

Petitioner proposes that a person of ordinary skill in the art of the '142 patent

would have possessed a strong understanding in the use and development of genetics and genomics approaches for detecting or monitoring human diseases, such as spatial detection of a target analyte (*e.g.*, mRNA or DNA) in a tissue, and would typically have a Ph.D. in a relevant field (*e.g.*, molecular biology, genetics, and bioinformatics) with two years of experience.

Pet. 21–22 (citing Ex. 1044 ¶¶ 24–36).

For the purposes of its Preliminary Response, Patent Owner does not provide its own proposed level of skill. Prelim. Resp. 7. For purposes of this Decision, we apply Petitioner's unchallenged definition as it is consistent with the cited prior art and disclosure of the '142 patent.

C. Claim Construction

Petitioner provides no claim construction for any term, but asks that we apply Patent Owner's interpretations of the '142 patent claims from the concurrent litigation. Pet. 22. Petitioner provides Patent Owner's infringement contentions (Ex. 1022) and pleading (Ex. 1038) from the litigation as evidence of Patent Owner's interpretations. Petitioner points us to Patent Owner's interpretation of "collecting" as used in independent claim 1, which Petitioner claims Patent Owner has interpreted to be "broad enough to encompass diffusion and capture of mRNAs across the *whole* tissue sample, all at the same time." Pet. 22 (citing Ex. 1022, 11–14, 18; Ex. 1044 ¶¶ 97, 100, 101, 199, 200).

Patent Owner states that it "does not dispute that the 'collecting' steps in claims 1 [and 16] includes the capture of mRNAs throughout the tissue

sample.” Prelim. Resp. 14. Patent Owner offers no claim constructions of its own. *See, generally*, Prelim. Resp.

For purposes of institution, we discern that we must interpret “synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction” and “identifying a first plurality [and second plurality] of DNA products by sequencing,” which we do so below in relation to Petitioner’s allegations of anticipation by Stahl.

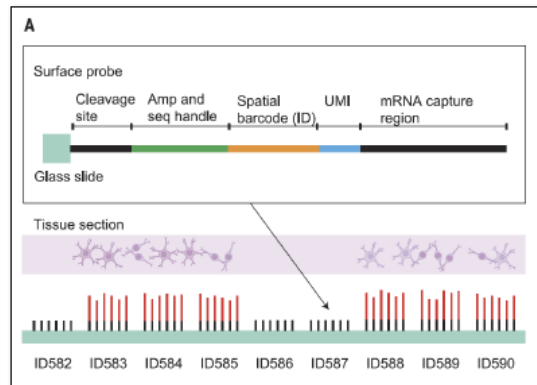
D. Anticipation by Stahl

Petitioner alleges that Stahl anticipates claims 1–4 and 6–13. Pet. 23–44.

1. Stahl (Ex. 1016)

Stahl is a journal article entitled “*Visualization and analysis of gene expression in tissue sections by spatial transcriptomics.*” At this stage of the proceeding, Patent Owner does not dispute the prior art status of Stahl. *See* Prelim. Resp. 13–14.

Stahl discloses a “spatial resolution” method, called “transcriptomics,” that “allows visualization and quantitative analysis” of the pattern of proteins or messenger RNAs present in individual tissue sections. Ex. 1016, 78. Stahl discloses the use of arrays of oligonucleotide “surface probes” immobilized in clusters on a glass slide, as shown in Figure 2A, replicated below:



Ex. 1016 at 80. Figure 2A, shown above, depicts an array (bottom) with unique DNA-barcoded surface probes immobilized on the array. *Id.* at Suppl. Materials, 2–3. The surface probes contain a cleavage site, an amplification and sequencing handle, a spatial barcode, a unique molecular identifier, and an oligonucleotide mRNA capture region. *Id.* The probes are immobilized to the array. *Id.* at 80. Each location on the array corresponds to a different “spatial barcode” that correlates the nucleic acid sequence to the location on the array. *Id.* at Abstract.

Stahl discloses placing a tissue slide across the array, followed by permeabilizing the tissue to permit mRNAs in the tissue to hybridize to the oligonucleotide mRNA capture region in the probes underneath the tissue. *Id.* at 80, Figure 2A. Once captured by a probe, a reverse transcription reaction is performed on the mRNA by a 3' extension of the capture probe to create cDNA, reflected by the red bars above in Figure 2A (“cDNA (red) is generated from captured mRNA by reverse transcription”). *Id.* at 80. The excess tissue is then removed from the array by enzymatic digestion, leaving behind the cDNAs bound to the capture probes on the slide. *Id.* at 78, Figure 1A.

After creating the cDNAs, Stahl discloses generating sequencing libraries by releasing the cDNAs from the capture probe, collecting the

cDNAs, incubating the cDNAs with amplification components, purifying the amplified RNA, and sequencing the amplified libraries on a commercial machine. *Id.* at Suppl. Materials 6–8. The sequencing data is processed to align the spatial barcodes with the location in the tissue of origin, permitting visualization of the location of the expressed mRNAs in the original tissue slide. *Id.* at 78, Figures 1A, 2A, Suppl. Materials, 1.

Stahl further discloses image comparison to visualize expression of the location of the amplified mRNAs (*id.* at 81, Figure 2B) and discloses incorporation of fluorescent tags during this process, to permit visualization of “fluorescent cDNA footprints” that allow identification of the location from which mRNA was isolated. *Id.* at Figure 1C, Suppl. Materials 8–9.

2. Disputed Issues

Petitioner alleges that Stahl anticipates claims 1–4 and 6–13. Pet. 23–44. Patent Owner disagrees and alleges that Stahl does not teach two limitations recited in challenged independent claim 1—“synthesizing DNA products” and “identifying the DNA products by sequencing.” Prelim. Resp. 14–27. Patent Owner focuses its arguments on these two limitations, and addresses only claim 1. *Id.* As Patent Owner does, we focus our discussion below on those limitations, but we discuss them in the order that the limitations are presented in claim 1.

a) Synthesizing DNA Products

(1) Allegations of the Parties

Patent Owner argues that Stahl does not disclose “synthesizing the DNA products” as recited in limitations c) and d) of claim 1. Prelim. Resp. 21–27. Patent Owner argues that Petitioner’s allegations fail to show that Stahl’s protocols “would result in incorporating the spatial address region

via a synthesis reaction.” *Id.* at 21. Patent Owner argues that Petitioner does not explain how the spatial barcode is incorporated by the reverse transcription reaction that uses captured mRNA as a template to make a cDNA product. *Id.* at 22. Patent Owner argues that because Stahl’s surface probe “already contains a spatial barcode—as acknowledged by Petitioner . . . there is no synthesis of cDNA that includes a spatial barcode.” *Id.* Patent Owner draws this distinction using an annotated excerpt of Figure 1A, shown below.

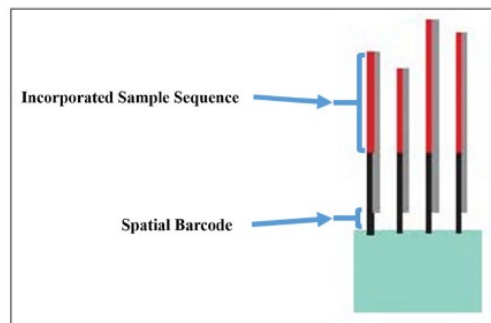


Figure 1A, annotated by Patent Owner to label the colored bars, depicts cDNA synthesis occurring on capture probes. Ex. 1016, 79, Figure 1A. Patent Owner argues that Petitioner identifies no other synthesis reaction achieving incorporation of the spatial barcode. *Id.* at 23–24.

We next turn to Petitioner’s allegations regarding how Stahl discloses “synthesizing the DNA products.”

Petitioner alleges that Stahl discloses synthesizing a first and second plurality of DNA products by performing a synthesis reaction “because Stahl’s method uses a reverse transcription reaction to ‘synthesize’ cDNA products using the captured mRNAs as templates.” Pet. 26 (citing Ex. 1044 ¶¶ 107–108). Petitioner cites as evidence Figure 1A of Stahl, reproduced below:

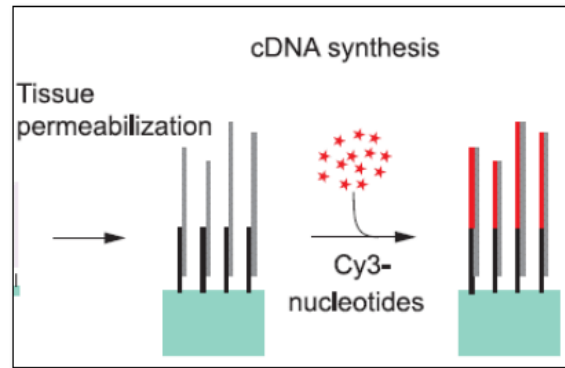


Figure 1A above depicts step one of spatially localized cDNA synthesis: “The tissue is sectioned, placed onto oligo(dT) primers, stained, and imaged. cDNA synthesis with Cy3-labeled nucleotides reveals fluorescent cDNA after tissue removal.” Ex. 1016, 79. Petitioner identifies the red bars in Figure 1A as evidence of cDNA synthesis and argues that Stahl discloses synthesis reactions incorporating identifying nucleic acids because Stahl “discloses that each capture probe on its array comprises a ‘spatial barcode,’ which is used to sort[] the RNA-seq data to its corresponding array features.” Pet. 28 (citing *id.*, 8, 80, Figure 2A; Ex. 1044, ¶¶ 112, 113). Petitioner argues that Stahl’s synthesis reaction “produces cDNA products comprising the spatial barcode of the capture probe, thus incorporating the spatial barcode” into the resulting cDNA products. *Id.* at 29 (citing Ex. 1016, Figures 1, 2, Suppl. Materials, 8 (referring to “barcoded cDNA”); Ex. 1044, ¶¶ 114–115).

In reply, Petitioner argues that Patent Owner’s position that Stahl does not teach the synthesis step because the capture probe of Stahl already comprised a spatial barcode sequence and thus is not incorporated by synthesis, is inconsistent with Patent Owner’s infringement contentions in the related litigation. Pet. PI Reply 3–5. There, Petitioner argues, Patent Owner alleged that a capture probe comprising a spatial barcode is used as a

primer and the captured sample mRNA as a template, resulting in the first cDNA products from the synthesis reaction comprising a spatial barcode in the same type of reaction taught in Stahl. *Id.* at 5 (citing Ex. 1016, 78–79, Figures 1, 2). Petitioner argues that although

PO’s infringement allegations point to both of [alleged infringer’s] synthesis steps, [these] cannot form the basis of PO’s infringement allegations because [they do] not use the “collected oligonucleotides” (i.e., captured sample mRNAs) as templates for the synthesis reaction, as required by claim 1.

Id. at 4–5.

In its sur-reply, Patent Owner argues that its identification of the “synthesis step” is not inconsistent between Patent Owner’s Preliminary Response and its infringement allegations in the related litigation. PO PI Sur-reply 3–5. Patent Owner argues that Petitioner only addresses part of Patent Owner’s infringement contentions with regard to synthesis, while ignoring others. *Id.* at 3–4. Patent Owner argues that its infringement contentions for the synthesis reaction “specifically refer to *both* [the accused product’s] steps 1 and 2.” *Id.* at 4 (citing Ex. 1022, 18–20; Paper 7, 4). Patent Owner argues that Petitioner’s own identification of Step 2 as not being able to form the basis of Patent Owner’s infringement allegations should be ignored. *Id.* Patent Owner argues that the distinction between its allegations against the accused product and the prior art asserted here are that “[the accused product] incorporates the spatial barcode by synthesizing the spatial barcode while Stahl and So-456 teach an extension from the capture probe that *does not* incorporate the spatial barcode via a synthesis reaction.” *Id.* at 5.

(2) *Analysis*

After review of the evidence of record, we conclude that it is necessary to interpret “synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction” for purposes of institution. Despite its importance to this issue, neither party has construed this phrase, although Petitioner suggests we use Patent Owner’s interpretations of the ’142 patent claims from the related litigation. Pet. 22 (citing Ex. 1022 (infringement contentions) and Ex. 1038 (pleading)). *See also* Pet. PI Reply, 4–5.⁵

To interpret “synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction” (“synthesizing DNA products”), we turn first to the words of claim 1 itself. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1301 (Fed. Cir. 2006) (“[C]laim construction must begin with the words of the claims themselves.”).

Claim 1 recites the following about “synthesizing DNA products”:

c) synthesizing a first/second⁶ 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;

Ex. 1043, 147:42–53.

⁵ With authorization (Paper 11), Petitioner filed a copy of the claim construction order entered by the district court in the related case (Ex. 1052). We address this order only with respect to a single claim term in Section II.G.2.B.2.

⁶ Claim elements c and d are grouped for brevity as the only different terms are “first” and “second.”

Thus, according to claim 1, to synthesize a first/second plurality of DNA products by performing a synthesis reaction, the “DNA products” must 1) use the oligonucleotides collected in steps (a) and (b) as templates from which the DNA is synthesized, and 2) incorporate a source location-identifying nucleic acid sequence.

Turning to the Specification, the text of the disclosure describes a method of spatially detecting a target analyte⁷ using sequencing of amplified nucleic acids as follows:

The present disclosure provides a method for spatially detecting at least one target analyte in at least one cell from a tissue sample comprising: (1) contacting at least one target analyte in at least one cell in a tissue sample with at least one probe comprising a target binding domain and an identifier oligonucleotide, wherein the identifier oligonucleotide comprises a unique nucleic acid sequence which identifies the target analyte bound to the target binding domain, a nucleic acid sequence comprising a unique molecular identifier, a first amplification primer binding site, and a second amplification primer binding site; (2) providing a force to a location of the tissue sample sufficient to release the identifier oligonucleotide; (3) collecting the released identifier oligonucleotide; (4) amplifying the released identifier oligonucleotide 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, wherein at least one of the amplification primers comprises a nucleic acid sequence which identifies the specific location of the tissue sample from which the identifier

⁷ The '142 disclosure patent states that “. . . a target analyte can be any molecule within a sample that is to be spatially detected. Target analytes include, but are not limited to, nucleic acid molecules . . . Target nucleic acids can include, but are not limited to . . . [genomic]DNA or any other nucleic acid present within a sample and protein molecules. Ex. 1043 47:33–43.

oligonucleotide was released; (5) Identifying the released identifier oligonucleotide by sequencing the amplified products produced in step (4), thereby spatially detecting the at least one target analyte in the at least one cell in a tissue sample.

Ex. 1043, 11:1–25.

Thus, the Specification informs us that “synthesizing DNA products” refers to amplifying collected identifier nucleotides released after application of a force (e.g., conditions that release the nucleic acid probes) from the location of the sample using primers that 1) have binding sites on the collected probe and 2) contain location-identifying nucleic acid sequences that are incorporated into the DNA product upon synthesis. *See id.*

Turning to other intrinsic evidence, the prosecution history does not have pertinent evidence regarding claim interpretation of *collecting* nucleic acid probes. *See generally*, Ex. 1014.

With this information in hand, we interpret “synthesizing DNA products.” “[C]laims are interpreted with an eye toward giving effect to all terms in the claim.” *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006).

Ultimately, the interpretation to be given a [claim] term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim. The construction that stays true to the claim language and most naturally aligns with the patent’s description of the invention will be, in the end, the correct construction.

Renishaw plc v. Marposs Societa per Azioni, 158 F.3d 1243, 1250 (internal citations omitted) (Fed. Cir. 1998).

We interpret “synthesizing DNA products” consistent with its usage in claim 1 as 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. We note that the Specification’s disclosure that amplification occurs using a primer with these sequences embedded suggests that the amplification of the collected oligonucleotide *directly* leads to a completed first DNA product containing location-identifying nucleic acid sequences, as Patent Owner argues is the case with the accused product in Patent Owner’s infringement contentions. *See* PO PI 3–5. However, Patent Owner’s use of “comprising” in claim 1 does not exclude additional steps such as an intermediary amplification. “The transition ‘comprising’ in a method claim indicates that the claim is open-ended and allows for additional steps.” *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003).

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. Ex. 1022, 9–12 (identifying “Step 1 Permeabilization and Reverse Transcription,” “Step 2 Second Strand Synthesis & Denaturation,” and “Step 3 Probe Release & Extension” as corresponding to the limitation “synthesizing DNA products”).

Accordingly, for purposes of this Decision, we apply this construction, and interpret “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. We note that this is a preliminary

construction because, at this stage of the proceeding, no other persuasive construction has been proposed by the parties.

The question then becomes whether Petitioner has shown a reasonable likelihood that Stahl, which teaches a two-step method of creating cDNA with identifying nucleic acids by reverse transcription, followed by generation of a second strand cDNA that incorporates a primer necessary to sequence the strand, anticipates “synthesizing DNA products” as recited in claim 1. On this record, for the reasons explained by Petitioner and as supported by its declarant testimony, we conclude Petitioner has sufficiently shown that Stahl discloses the “synthesizing DNA products” limitation recited in claim 1.

b) Identifying the DNA Products by Sequencing

(1) Allegations of the Parties

Patent Owner argues that Stahl does not disclose “identifying the first plurality of DNA products and the second plurality of DNA products . . . by *sequencing*” because Stahl’s method does not sequence the first-strand cDNA that Petitioner identifies as the DNA product. Prelim. Resp. 15–20 (citing Pet. at 26). Patent Owner argues that Stahl discloses generation of a second strand cDNA from the first strand cDNA, followed by amplification of the second strand cDNA to add sequences (“ligation adapters”) necessary for sequencing of the second strand cDNA. *Id.* at 16–18. Patent Owner argues that the second strand cDNA, which is the DNA product that is sequenced, is “*not* the first cDNA products purported by Petitioner to be the ‘DNA products’ required by the ’142 Patent.” *Id.* at 18. According to Patent Owner, because it is this second cDNA strand that is sequenced, Stahl does not disclose identifying the DNA product by sequencing, but rather the

sequencing of a different, downstream product, the second cDNA strand. *Id.* at 18–19.

We next turn to Petitioner’s allegations regarding how Stahl discloses “identifying the DNA products by sequencing.”

Petitioner argues that Stahl discloses generating sequence libraries from the collected spatially barcoded cDNA synthesis products, then amplifying and sequencing the products. Pet. 30 (citing Ex. 1016, Suppl. Materials, 6–7; Ex. 1044, ¶¶ 117–118). Petitioner argues that Stahl discloses identifying the cDNA synthesis products in this manner because “Stahl explains that the sequencing (‘RNA-seq’) data was ‘sorted ... to its corresponding array features by *using the spatial barcodes*,’ which ‘enabled visualization and analyses.’” *Id.* (citing Ex. 1016, 78; Ex. 1044, ¶¶ 117–118). In arguing that Stahl’s method of spatial detection of the oligonucleotides collected from the tissue sample is anticipatory, Petitioner applies Patent Owner’s agreed-to definition in the related litigation, where the parties stipulated that “‘spatially detecting’ means ‘identifying the presence of a specific target analyte within a specific region of interest in a sample.’” *Id.* at 29 (citing Ex. 1024, 31; Ex. 1044, ¶ 116). Petitioner points to Figure 2B of Stahl as evidence of “depicting visualization and expression of three genes in mouse olfactory bulb tissue (upper), which Stahl confirmed with in situ hybridization (bottom).” *Id.* at 30–31 (citing Ex. 1016, Figure 2B). Figure 2B of Stahl is reproduced below.

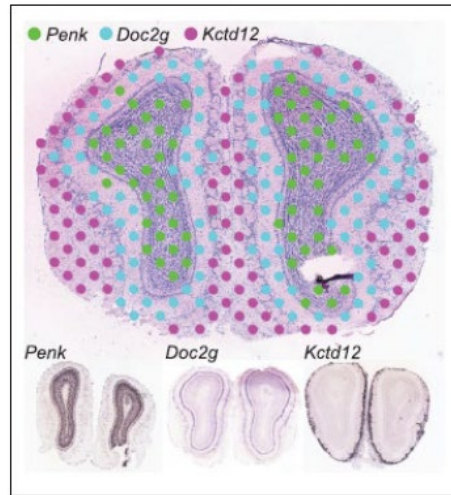


Figure 2B, entitled “Spatially resolved gene expression” depicts the “Visualization of the expression of three genes by spatial transcriptomics (top) and in situ hybridization (bottom).” Ex. 1016, Figure 2B.

In reply, Petitioner argues that Patent Owner’s position that Stahl does not teach the sequencing step because Stahl’s method does not sequence the first strand cDNA product that was reverse transcribed from the sample mRNA, is inconsistent with its infringement contentions in the related litigation, where Patent Owner alleged that the identifying DNA products by sequencing step “*encompasses* sequencing DNA products that are generated downstream of the first cDNA products (which were reverse transcribed from the collected sample mRNAs).” Pet. PI Reply, 2 (citing Ex. 1022, 22–24).

In its sur-reply, Patent Owner argues that its identification of the “sequencing step” is not inconsistent between its Preliminary Response and its infringement allegations in the related litigation. PO PI Sur-reply 1. Patent Owner argues that Petitioner characterizes Patent Owner’s infringement contentions in the related case to be broader than they are. *Id.* at 1–3. Patent Owner argues that it did not identify the reverse transcription

of the collected nucleotides as the sequencing step in the related litigation, but rather “steps 4 (‘Visium Spatial Gene Expression Library Construction’) and 5 (‘Sequencing’) for sequencing the ‘DNA products.’” PO PI Sur-reply 2 (citing Ex. 1022, 18–20, 22–24). Patent Owner argues that Petitioner inconsistently identifies DNA products as being the product of the DNA sequencing step in two different respective stages in Stahl and So-456, and that Petitioner should not be permitted to make inconsistent allegations. *Id.* at 3.

(2) *Analysis*

After review of the evidence of record, we conclude that it is necessary to interpret “identifying a first plurality [and second plurality] of DNA products by sequencing” for purposes of institution. Again, neither party has expressly construed this phrase, although Petitioner suggests we use Patent Owner’s interpretations of the ’142 patent claims from the related litigation. Pet 22 (citing Ex. 1022 (infringement contentions) 11–14). *See also* Pet PI Reply, 1–3. In those contentions, Patent Owner identified as infringing a product that, using a multi-step process, generated sequencing libraries from cDNA that was reverse transcribed from sample mRNA, sequenced the product, and mapped the product for spatial gene expression using spatial barcodes. Ex. 1022, 18–19, 22–24.

To interpret “identifying a first plurality [and second plurality] of DNA products by sequencing” (“identifying DNA products”), we turn first to the words of claim 1 itself. *Amgen*, 457 F.3d at 1301.

Claim 1 recites the following about “identifying DNA products”:

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.

Ex. 1043, 147:54–61.

According to the language of claim 1, identifying a first/second plurality of DNA products by sequencing the products is the final step in the method of spatially detecting the source of the collected oligonucleotides. The claim language does not provide additional information as to the meaning of identifying the DNA products.

Turning to the Specification, we find no helpful disclosure explaining “identifying the DNA products.” In general, uses of “identifying” in the Specification refer to collected oligonucleotides that are amplified and then sequenced as a final step in the method of “spatially detecting.” *See, e.g.*, 1:64–67, 2:50–54, 4:66–5:2; 9:55–58. Again, the Specification informs us that “identifying the DNA products” is the final method step of spatially detecting the collected identifier nucleotides.

Turning to other intrinsic evidence, the prosecution history does not have pertinent evidence regarding claim interpretation of identifying the DNA products. *See generally*, Ex. 1014.

We also note the parties’ stipulation that “spatially detecting” means “identifying the presence of a specific target analyte within a specific region of interest in a sample.” Ex. 1024, 31.

In claim 1, the steps of the method prior to the identifying step have performed collection of oligonucleotides and creation of DNA products from them that contain location-identifying nucleic acid sequences. The remaining step is then to correlate the DNA product using the location-

identifying nucleic acid sequences with the source of the original mRNA, thereby locating the specific target analyte.

We interpret “identifying the DNA products,” consistent with its usage in claim 1 as “locating the specific target analyte within the tissue sample by correlating the DNA product using the location-identifying nucleic acid sequences.” Our interpretation is consistent with the Specification’s disclosure concerning “identifying” stated above, and also consistent with the stipulation of the parties and Patent Owner’s infringement contentions, where Patent Owner identifies “identifying the DNA products” as covering the use of spatial barcodes in amplified cDNA-generated libraries to “associate the reads back to the tissue section images for spatial gene expression mapping.” Ex. 1022, 22–24.

Accordingly, for purposes of this Decision, we apply this construction, and interpret “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. We note that this is a preliminary construction because, at this stage of the proceeding, no other persuasive construction has been proposed by the parties.

The question then becomes whether Petitioner has shown a reasonable likelihood that Stahl, which teaches a two-step method of creating cDNA with identifying nucleic acids by reverse transcription, followed by generation of a second strand cDNA that incorporates a primer necessary to sequence the strand, anticipates “synthesizing DNA products” as recited in claim 1. On this record, for the reasons explained by Petitioner and as supported by its declarant testimony, we conclude Petitioner has sufficiently shown that Stahl discloses the “synthesizing DNA products” limitation

recited in claim 1, particularly as this interpretation is consistent with Patent Owner's application of the scope of the limitation in infringement contentions in the related litigation. *See* Ex. 1022, 22–24.

E. Obviousness over Stahl

1. Allegations of the Parties

Petitioner alleges that, to the extent Stahl does not anticipate claims 1–4, and 6–13, Stahl renders those claims obvious. Pet. 44–45 (citing Ex. 1044 ¶¶ 160–164). Petitioner also alleges that claim 5 would have been obvious over Stahl. *Id.* at 45–49 (citing Ex. 1044 ¶¶ 107–115, 166–178).

Patent Owner disagrees, and argues that Petitioner does not support its case for obviousness of the challenged claims, and focuses on the same two limitations that Patent Owner addressed with respect to anticipation. Prelim. Resp. 25–27. Patent Owner raises no argument specific to claim 5. *Id.*

2. Analysis

For the reasons stated above in section II.D., we conclude that Petitioner has sufficiently shown for institution purposes that the teachings of Stahl render at least claim 1 unpatentable for anticipation, which would equally apply to obviousness. “It is well settled that ‘anticipation is the epitome of obviousness.’” *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). Because we institute on all claims and all grounds, *PGS Geophysical v. Iancu*, 891 F.3d at 1360, Patent Owner's arguments related to nonobviousness of claim 5 are best left for a fully developed record.

F. Obviousness over Stahl and Frisen

1. Frisen (Ex. 1017)

Frisen is a PCT application entitled “Method and Product for Localised or Spatial Detection of Nucleic Acid in a Tissue Sample.” Patent Owner does not dispute the prior art status of Stahl. *See* Prelim. Resp. 13–14. Frisen is directed to a method for “spatial transcriptomics” or “spatial genomics” and discloses spatially detecting nucleic acids in a tissue sample using a spatially barcoded array. Ex. 1017, Abstract, 1:12–33.

2. Disputed Issues

Petitioner alleges claim 5 is obvious over Stahl and Frisen. Pet. 49–56. Patent Owner does not offer any arguments regarding claim 5 or this ground. *See, generally*, Prelim. Resp.

3. Analysis

For the reasons stated above in section II.D., we conclude that Petitioner has sufficiently shown for institution purposes that the teachings of Stahl render at least claim 1 unpatentable for anticipation. Arguments related to claim 5 are best left for a fully developed record.

G. Anticipation by So-456

1. So-456 (Ex. 1005)

So-456 is a published patent application directed to “methods and compositions for spatial detection and analysis of nucleic acids in a tissue sample.” Ex. 1005, Abstract. Patent Owner does not dispute the prior art status of So-456. *See* Prelim. Resp. 10–13.

So-456 discloses that its methods provide for “characterization of analytes in tissues while preserving spatial information related to the origin of target analyte in the tissue.” *Id.* ¶ 85. Specifically, “spatial addressing of

nucleic acids from a tissue sample can involve two-dimensional spatial addressing, e.g., to correlate the position of a nucleic acid on a two-dimensional capture array with the position of the nucleic acid in a two-dimensional tissue section.” *Id.* ¶ 94. So-456 discloses the method steps in Figure 2, reproduced below:

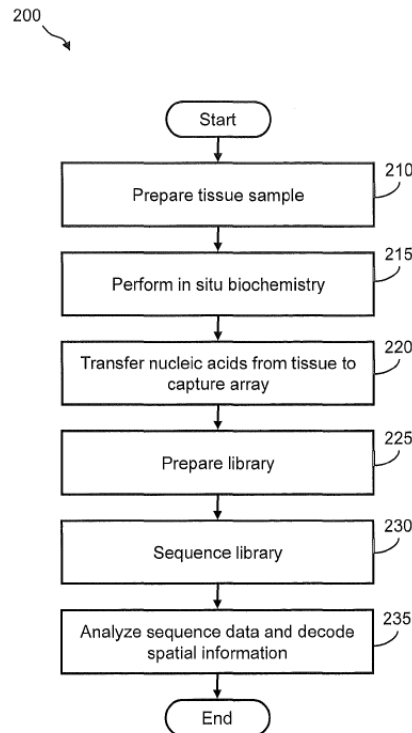


Figure 2 “illustrates a flow diagram of an exemplary embodiment of a method of spatial detection and analysis of nucleic acid in a tissue sample.” *Id.* ¶ 12.

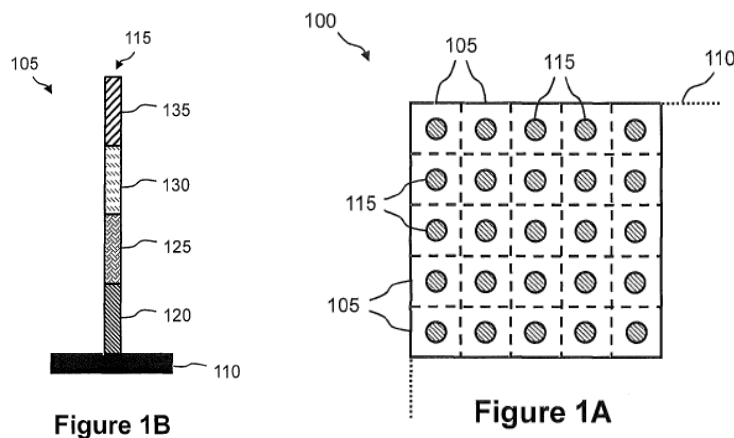
So-456 discloses encoding information identifying the spatial origin of a nucleic acid in a tissue sample during the process of preparing the nucleic acid for sequencing:

nucleic acids from a tissue sample can be tagged by probes including location-specific sequence information (a “spatial address”). Spatially addressed nucleic acid molecules from a tissue sample can then be sequenced in bulk. The sequence-identical nucleic acid molecules originating from different

regions in a tissue sample can be distinguished based on their spatial address and can be mapped onto their regions of origin in the tissue sample.

Id. ¶ 89.

So-456 discloses a “capture probe” as shown below in Figure 1B, which is used to capture the nucleic acids or “DNA amplicons” in a sample that are generated by in situ amplification of [a] target nucleic acid, and then analyzed on a “capture array,” also shown below in Figure 1A. *Id.* ¶ 18.



Reproduced above is Figure 1B, a “side view of one capture site of the capture array, wherein the one capture site comprises at least one capture probe for capture of nucleic acid in a tissue sample.” *Id.* ¶ 10. “Capture probe 115 may optionally comprise a cleavable sequence in a cleavable region 120, an SBS [sequencing-by-synthesis] primer sequence in a SBS primer binding site 125, a spatial address sequence in a spatial address region 130, and a capture sequence in a capture region 135.” *Id.* ¶ 141.

Also reproduced above is Figure 1A illustrates a “plan view of an exemplary embodiment of a capture array for capture of nucleic acid in a tissue sample.” *Id.* ¶ 9. Capture probe 115 is “immobilized” at each of the capture sites 105 of capture array 100, meaning it is fixed by “direct or

indirect attachment to a solid support via covalent or non-covalent bond(s).”
Id. ¶¶ 109, 141.

Figures 8 and 9, reproduced below, illustrate a flow diagram (Figure 8) and an exemplary embodiment (Figure 9) of the method of creation of and capture of DNA amplicons generated in by in situ amplification of target nucleic acids.

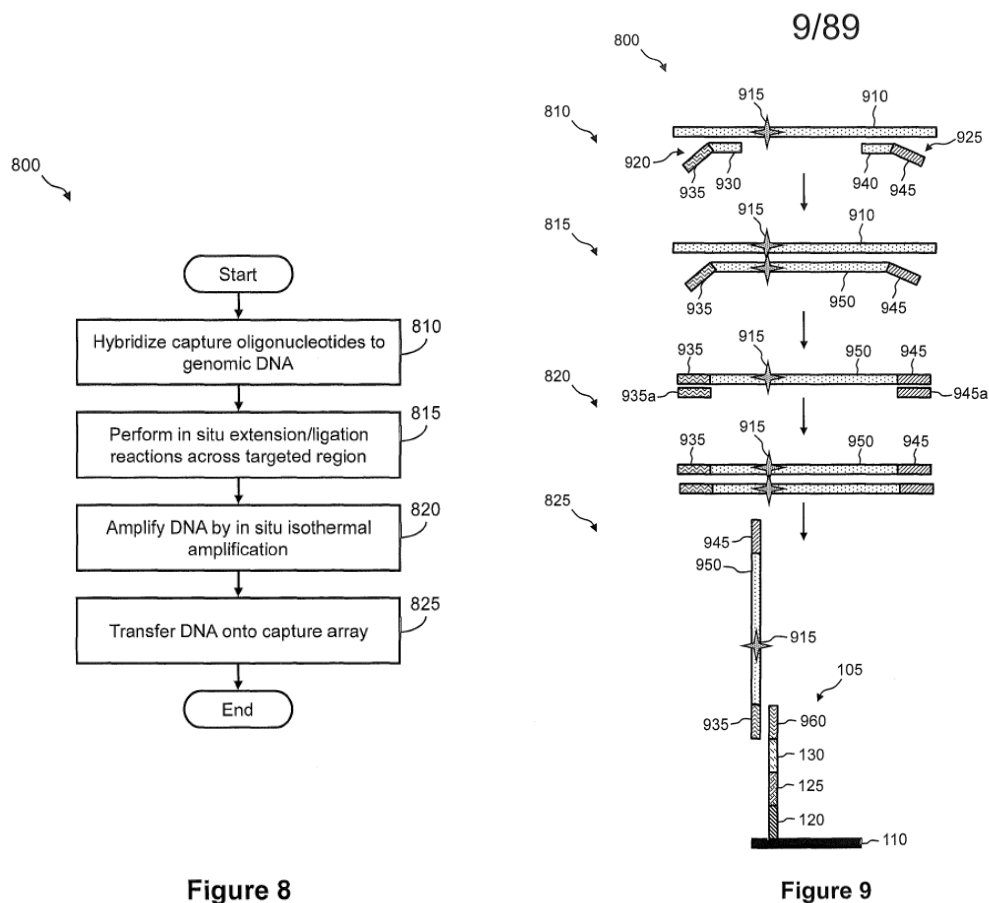


Figure 8, reproduced above, is a flow diagram of the method of creation of and capture of DNA amplicons generated in by in situ amplification of target nucleic acids. *Id.* ¶ 19. Figure 9 illustrates an embodiment of the method of capturing DNA amplicons onto an array, wherein the DNA amplicons are generated by in situ amplification of target nucleic acid. *Id.* ¶¶ 18, 19. “At a step 810, a pair of gene-specific capture oligonucleotides that flank a region

of interest [915] are hybridized in situ to genomic DNA.” *Id.* ¶ 178. The capture oligonucleotides contain “a gene-specific sequence and a universal capture sequence.” The capture nucleotide binds (ligates) to the region of interest and the DNA flanked by capture oligonucleotides having bound at the 3’ and 5’ ends of the target DNA “is amplified by in situ isothermal amplification to generate multiple copies of the region of interest, i.e., multiple genomic amplicons.” *Id.* ¶¶ 179, 180. Genomic amplicons are collected and transferred to an array for capture by hybridization to universal capture regions on the array. *Id.* ¶ 181.

As shown in Figure 9, “capture probe 115 on the capture site 105 comprises a capture region 960 that is complementary to universal capture region 935; SBS primer region 130 is SBS3. DNA amplicons 950 are captured on the capture site 105 by hybridization of universal capture region 935 to capture region 960.” *Id.* ¶¶ 182, 183. Following capture, the ligation products can undergo an extension reaction to tag the products with spatial barcodes or generate additional molecules for analysis. *Id.*, Figure 6, ¶¶ 173, 174, 182).

2. *Disputed Issues*

Petitioner alleges that So-456 discloses all limitations of challenged claims 1–13. Pet. 56–77. Patent Owner disagrees and alleges that So-456 does not teach three limitations recited in the challenged claims. Prelim. Resp. 27–42. Patent Owner focuses its arguments on independent claim 1. *Id.* As Patent Owner does, we focus our discussion below on the limitations of claim 1 that Patent Owner claims So-456 does not teach.

a) Identifying the DNA products by sequencing
(1) Allegations of the parties

Patent Owner argues that So-456 does not disclose “identifying the DNA products by sequencing” because So-456’s method does not sequence the first-strand cDNA that Petitioner identifies as the DNA product. Prelim. Resp. 28–29 (citing Pet. 61). Patent Owner argues that So-456 discloses generation of a second strand cDNA from the first strand cDNA, followed by amplification of the second strand cDNA to add sequences necessary for sequencing of the second strand cDNA. *Id.* at 31–32. Patent Owner emphasizes that, rather than being a duplicate of the first strand cDNA, the second strand cDNA contains two unique sequences for capture probes and two unique spatial address sequences for the X and Y dimension, respectively, and a SBS3 and SBS12 sequence. *Id.* at 32 (citing Ex. 1005 ¶ 319). According to Patent Owner, because it is this second cDNA strand that is sequenced, So-456 does not disclose identifying the DNA product by sequencing, but rather a different, downstream product, the second cDNA strand. *Id.* at 32.

We next turn to Petitioner’s allegations regarding how So-456 discloses “identifying the DNA products by sequencing.”

Petitioner alleges that So-456 discloses synthesizing first-strand cDNA molecules by amplification on an array to create second-strand cDNA, followed by processing to generate a sequencing library. Pet. 65 (citing Ex. 1005, ¶¶ 310–313, 317–320; Ex. 1044, ¶ 217). Petitioner argues that the second strand cDNA molecules are released and comprise the spatial address region of the first capture probe. *Id.* at 65–66 (citing Ex. 1005, ¶ 319; Ex. 1044, ¶ 217).

Petitioner further argues that So-456 discloses that the second-strand cDNA molecules are amplified to create a sequencing library, which is analyzed to decode the spatial information to inform the user of the location of the collected nucleic acid within the tissue section. *Id.* at 66 (citing Ex. 1005, ¶¶ 313, 320). Petitioner argues that So-456 discloses the ability to map spatial addresses onto the location of the tissue sample, to allow identification of the cell or cell cluster in the tissue sample, thereby identifying the DNA products. *Id.* (citing Ex. 1005, ¶¶ 2, 88; Ex. 1044, ¶ 219).

In arguing that So-456's method of spatial detection of the oligonucleotides collected from the tissue sample is anticipatory, Petitioner applies Patent Owner's agreed-to definition in the related litigation, where the parties stipulated that "'spatially detecting' means 'identifying the presence of a specific target analyte within a specific region of interest in a sample.'" *Id.* at 65 (citing Ex. 1024, 31; Ex. 1044, ¶ 216).

In reply, Petitioner argued that Patent Owner's position that So-456 does not teach the synthesis step because its methods sequence products that are generated after the first cDNA product rather than from the first cDNA product is inconsistent with Patent Owner's infringement contentions in the related litigation. Pet. PI Reply 1–3. There, Petitioner argues, Patent Owner alleged that claim 1's sequencing step covered sequencing DNA products generated beyond the first cDNA product, just as So-456 discloses. *Id.* (citing Ex. 1022, 22–24).

In its sur-reply, Patent Owner argues that its identification of the "sequencing step" is not inconsistent between its Preliminary Response and its infringement allegations in the related litigation. PO PI Sur-reply 1.

Patent Owner argues that Petitioner characterizes Patent Owner's infringement contentions in the related case to be broader than they are. *Id.* at 1–3. Patent Owner argues that it did not identify the reverse transcription of the collected nucleotides as the sequencing step in the related litigation, but rather “steps 4 (‘Visium Spatial Gene Expression Library Construction’) and 5 (‘Sequencing’) for sequencing the ‘DNA products.’” *Id.* at 2 (citing Ex. 1022, 18–20, 22–24). Patent Owner argues that Petitioner inconsistently identifies DNA products as being the product of the DNA sequencing step in two different respective stages in Stahl and So-456, and that Petitioner should not be permitted to make inconsistent allegations. *Id.* at 3.

(2) *Analysis*

As discussed above, we construed “identifying the DNA products by sequencing” to mean “locating the specific target analyte within the tissue sample by correlating the DNA product using the location-identifying nucleic acid sequences.” *Supra*, Section II.D.2(b)(2). Applying this construction, and on this record, for the reasons explained by Petitioner and as supported by its declarant testimony, we conclude Petitioner has sufficiently shown for institution purposes that So-456 discloses the “identifying DNA products by sequencing” limitation recited in claim 1, particularly as this interpretation is consistent with Patent Owner's application of the scope of the limitation in infringement contentions in the related litigation. *See* Ex. 1022, 22–24.

(3) *Synthesizing DNA Products*

(a) *Allegations of the parties*

Patent Owner argues that So-456 does not disclose synthesizing the DNA products as recited in limitations c) and d) of claim 1. Prelim. Resp. 33–38. Patent Owner argues that Petitioner’s allegations fail to show that So-456 discloses incorporation of a nucleic acid sequence that identifies the location of the source of the nucleic acid. *Id.* at 33. Patent Owner argues that Petitioner does not explain how the spatial barcode is incorporated by the reverse transcription reaction that uses captured mRNA as a template to make a cDNA product. *Id.* at 34. Patent Owner argues that because So-456’s capture probe already contains a spatial address region, there is no “synthesis” step that adds the spatial address, and that while the resulting products as amplified may contain the spatial address region, it was not added through a synthesis reaction. *Id.* Patent Owner draws this distinction using excerpts of Figures 25A and 25B, shown below.

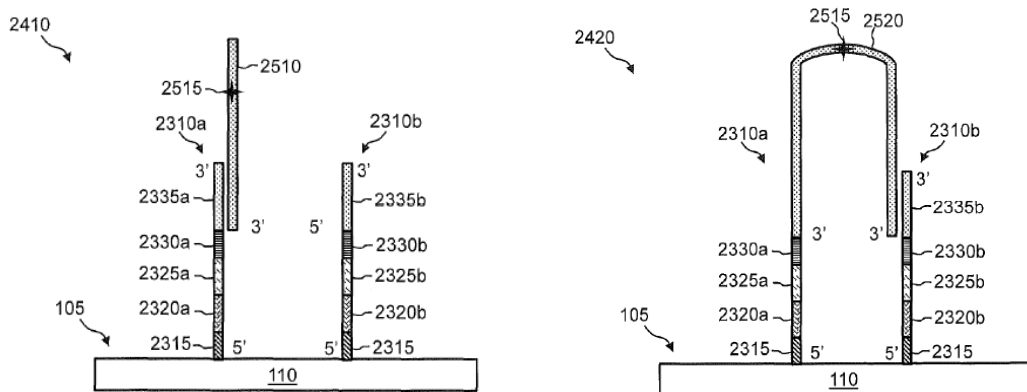


Figure 25A illustrates “a single capture site 105 of capture array 100. Ex. 1005 ¶ 314. A “mRNA molecule 2510 in a tissue sample is captured on capture probe 2310a.” *Id.* ¶ 315. Figure 25B illustrates how “second strand cDNA is synthesized in an extension reaction using capture region 2335b as a primer.” *Id.* ¶ 318. Patent Owner argues that the capture probe includes a

purported spatial address region, 2325a. Prelim. Resp. 35 (citing Ex. 1005 ¶ 319). Patent Owner argues that because the spatial address region is not incorporated into the cDNA synthesized from the oligonucleotide, that the “synthesized” portion of the claim limitation is not met. *Id.* at 36–38.

We next turn to Petitioner’s allegations regarding how So-456 discloses “synthesizing the DNA products.”

Petitioner alleges that So-456 discloses that the capture probes comprise a spatial address region with a unique spatial address sequence, and resides on the capture probe at 2325a in the Figures shown above. Pet. 63–62 (citing Ex. 1005 ¶ 141, Figure 25B; Ex. 1044 ¶ 214). Petitioner’s declarant opines that the first strand cDNA (2520) is synthesized using the first capture probe (3130a) as a primer and the mRNA as a template, and thus, when amplified, comprises the spatial address region. *Id.* (citing at Ex. 1004 ¶ 214).

In reply, Petitioner argues that Patent Owner’s position that So-456 does not teach the synthesis step because the capture region of So-456 already comprised a spatial barcode sequence and thus is not incorporated, is inconsistent with Patent Owner’s infringement contentions in the related litigation. Pet. PI Reply 3–5. There, Petitioner argues, Patent Owner alleged that a capture probe comprising a spatial barcode is used as a primer and the captured sample mRNA as a template, resulting in the first cDNA products from the synthesis reaction comprising a spatial barcode in the same type of reaction taught in So-456. *Id.* at 5 (citing Ex. 1022, 18–20, 22).

In its sur-reply, Patent Owner argues that its identification of the “synthesis step” is not inconsistent between Patent Owner’s Preliminary Response and its infringement allegations in the related litigation. PO PI

Sur-reply 3–5. Patent Owner argues that Petitioner only addresses part of Patent Owner’s infringement contentions with regard to synthesis, while ignoring others. *Id.* at 3–4. Patent Owner argues that its infringement contentions for the synthesis reaction “specifically refer to *both* [the accused product’s] steps 1 and 2.” *Id.* at 4 (citing Ex. 1022, 18–22; Paper 7, 4). Patent Owner argues that Petitioner’s own identification of Step 2 as not being able to form the basis of Patent Owner’s infringement allegations should be ignored. *Id.* Patent Owner argues that the distinction between its allegations against the accused product and the prior art asserted here are that “[the accused product] incorporates the spatial barcode by synthesizing the spatial barcode while Stahl and So-456 teach an extension from the capture probe that *does not* incorporate the spatial barcode via a synthesis reaction.” *Id.* at 5.

(b) Analysis

As discussed above, we interpret “synthesizing DNA products” consistent with its usage in claim 1 as 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. Section II.D.2(b)(2). For purposes of this Decision, we apply this construction, and next consider whether So-456, which teaches a two-step method of creating cDNA with identifying nucleic acids by reverse transcription, followed by generation of a second strand cDNA that incorporates a primer necessary to sequence the strand, anticipates “synthesizing DNA products” as recited in claim 1. On this record, for the reasons explained by Petitioner and as

supported by Petitioner's declarant's testimony, we conclude Petitioner has sufficiently shown that So-456 discloses the "synthesizing DNA products" limitation recited in claim 1.

b) Collecting oligonucleotides under conditions that release them

(1) Allegations of the Parties

Patent Owner argues that So-456 does not disclose collecting nucleotides under conditions that release them as recited in claim 1. Prelim. Resp. 38–42. Patent Owner argues that So-456 discloses that the tissue sample from which oligonucleotides must be collected is sectioned, stained, and fixed in paraffin, and is thus not in the condition to release oligonucleotides from the sample. *Id.* at 39 (citing Ex. 1005 ¶ 125). Rather, Patent Owner argues that So-456 describes transferring oligonucleotides in a tissue sample that has been fixed in paraffin and that Petitioner's allegations do not specify how this issue is overcome. *Id.* at 39–41.

We next turn to Petitioner's allegations regarding how So-456 discloses "collecting oligonucleotides under conditions that release them." Petitioner alleges that So-465 teaches collecting a plurality of oligonucleotides from a first and second location within the tissue slide by contacting it with a capture array containing capture probes containing sequences that hybridize with the mRNA gene-specific regions. Pet. 57–58 (citing Ex. 1005 ¶¶ 308, 314, 315, Figures 24, 25A, Ex. ¶ 201). Petitioner argues the capture array correlates the position of the nucleic acid with the position on the tissue sample, and that collection of mRNAs occurs simultaneously at multiple locations of the tissue sample and thus at multiple capture sites on the array. *Id.* at 59–60 (citing Ex. 1005 ¶¶ 141, 154, 205, 307, 308, 314, 315). Petitioner argues that So-456's disclosure that the

“tissue sample is prepared for analysis” resulting in capture of mRNAs on the array shows that the nucleic acids were released, meaning that the tissue was treated to release the nucleic acids. *Id.* at 60–61.

(2) Analysis

Neither party has offered a construction for “collecting oligonucleotides under conditions that release them” in claim 1. We note that, in the related litigation, the district court determined that “under conditions that release” should have its plain and ordinary meaning. Ex. 1052, 38. For purposes of institution, we also apply the plain and ordinary meaning of this claim phrase and do not need to expressly construe the claim phrase for purposes of institution. On this record, for the reasons explained by Petitioner and as supported by its declarant testimony, we conclude Petitioner has sufficiently shown that So-456 discloses the “collecting oligonucleotides under conditions that release them” limitation recited in claim 1.

H. Obviousness over So-456

1. Allegations of the Parties

Petitioner alleges that, to the extent So-456 does not anticipate claims 1–13, So-456 renders all of claims 1–13 obvious. Pet. 77–79 (citing Ex. 1044 ¶¶ 253–256).

Patent Owner disagrees, and argues against obviousness concurrently with its argument regarding the same three limitations that Patent Owner addressed with respect to anticipation. Prelim. Resp. 27–42.

2. *Analysis*

For the reasons stated above in section II.G., we conclude that Petitioner has sufficiently shown for institution purposes that the teachings of So-456 render at least claim 1 unpatentable for anticipation, which would equally apply to obviousness. *McDaniel*, 293 F.3d at 1385. Because we institute on all claims and all grounds, *PGS Geophysical v. Iancu*, 891 F.3d at 1360, Patent Owner's arguments related to obviousness are best left for a fully developed record.

III. CONCLUSION

For the reasons expressed above, we determine that Petitioner has demonstrated a reasonable likelihood of showing that at least one claim of the '142 patent is unpatentable. As set forth in the Order below, we institute a trial on all challenged claims and all asserted grounds of unpatentability. *See* 37 C.F.R. § 42.108(a) ("When instituting *inter partes* review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim.").

Our factual findings and determinations at this stage of the proceeding are preliminary, and based on the evidentiary record developed thus far. This is not a final decision as to the patentability of claims for which *inter partes* review is instituted. Our final decision will be based on the record as fully developed during trial.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, an *inter partes* review is instituted as to all challenged claims on all the grounds raised in the Petition; and

FURTHER ORDERED that *inter partes* review is instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

IPR2023-01300
Patent 11,473,142 B2

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