

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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10X GENOMICS, INC.,  
Petitioner,

v.

NANOSTRING TECHNOLOGIES, INC.,  
Patent Owner.

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IPR2023-01298  
Patent No. 11,377,689 B2

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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 Petition for *inter partes* review of claims 1–30 of U.S. Patent No. 11,377,689 B2 (“the ’689 patent”). Paper 2 (“Pet.”). Patent Owner NanoString Technologies, Inc., (“Patent Owner”) filed a Preliminary Response (Paper 8, “Prelim. Resp.”).

With our authorization (Order, Paper 9), Petitioner filed Petitioner’s Pre-Institution Reply (Paper 11, “Pet. PI Reply”) and Patent Owner filed Patent Owner’s Pre-Institution Sur-Reply (Paper 12, “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 based on the last ground presented by Petitioner. Accordingly, we institute an *inter partes* review of the challenged claims in the Petition.

#### *B. Real Parties in Interest*

Petitioner and Patent Owner identify themselves as the real parties-in-interest. Pet. 77; Paper 4, 1 (Patent Owner’s Mandatory Notice).

#### *C. Related Matters*

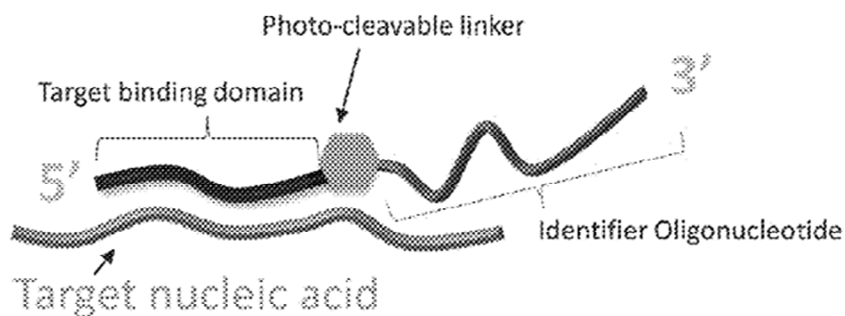
Petitioner identifies a related litigation in which the ’689 patent was asserted, *10x Genomics, Inc. and President and Fellows of Harvard College v. NanoString Technologies, Inc.*, Case No. 1:22-cv-00261 (D. Del.). Pet. 78. Petitioner indicates that, following assertion of the ’689 patent in that case, “the 689 patent counterclaim was severed from Case No. 1:22-cv-00261 and consolidated with *NanoString Technologies, Inc. v. 10x Genomics, Inc.*, Case No. 1:22-cv-01375 (D. Del.).” *Id.*

Patent Owner identifies the same matters. Paper 4, 2.

*D. The '689 Patent*

The '689 patent issued on July 5, 2022, from U.S. Appl. No. 17/476,707 ("707 application"), filed September 16, 2021. Ex. 1001, codes (45), (21), (22). The 707 application is a continuation of U.S. Appl. No. 16/272,487 ("487 application"; Ex 1009), filed on February 11, 2019, which claims priority to U.S. Appl. Nos. 62/771,212 (Ex. 1010), filed November 26, 2018, and 62/629,180 (Ex. 1011), filed February 12, 2018. Ex. 1001, codes (63), (60).

The '689 patent is directed to a method for spatially detecting nucleic acids in a tissue sample. *Id.* at 1:44–67. The method uses nucleic acid probes to bind to target nucleic acids ("analytes") within a tissue sample that has been treated to permit binding. *Id.* at 1:44–67; 145:57–58; 148:1–4. The probes 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 a region of the probe that specifically binds to at least one target analyte in a sample." *Id.* at 37:16–17. Multiple locations may be probed within the tissue sample using different nucleic acid

probes. *Id.* at 33:33–49. In some embodiments, the probes are bound to the target binding domain, and then ligated to each other, to permit amplification of the target binding domain. *See, e.g., id.* at 6:2–5; 148:5–11.

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 39:16–18. In one embodiment, the linker permits release of the identifier oligonucleotide when exposed to a sufficient wavelength of ultraviolet 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.”<sup>1</sup> *Id.* at 38:29–33.

Figure 20, reproduced below, is a schematic overview of the method of the ’689 patent.

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<sup>1</sup> Such unique identifying sequences in the references at issue are called unique molecular identifiers (UMIs), unique nucleic acid sequences, and spatial addresses or spatial barcodes, depending on the reference. *See, e.g.,* Ex. 1001, 38:29–33 (unique nucleic acid sequence); Ex. 1005 ¶ 98 (spatial address), and Ex. 1016, 80. (UMI). We understand these various phrases to refer to the use of a nucleic acid with a unique sequence used to identify the source of target DNA.

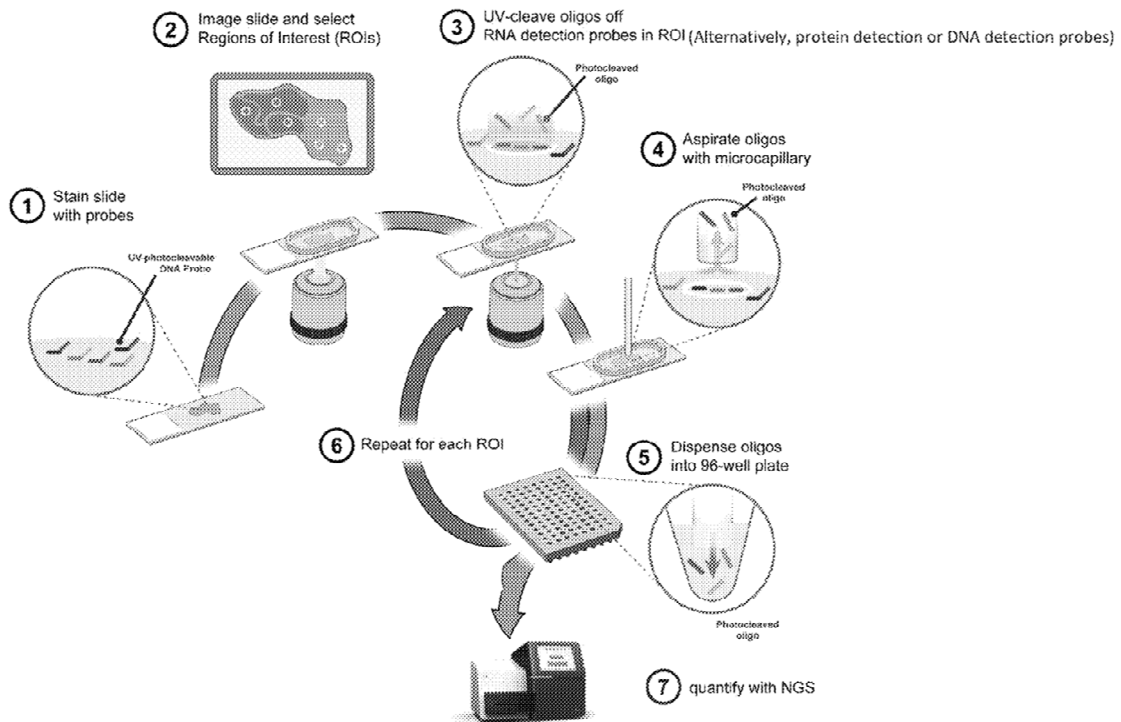


FIG. 20 is an exemplary schematic of overview of the methods of the present disclosure. First, a sample on a microscope slide is contacted with a plurality of probes of the present disclosure (step 1 in FIG. 20). The slide is then imaged and particular regions of interest (ROIs) are selected (step 2 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 36:62–37:11.

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 32:27–51. Figure 11, reproduced below, depicts an embodiment in which the identifier nucleotide is amplified, including the portion comprising the unique nucleic acid sequence.

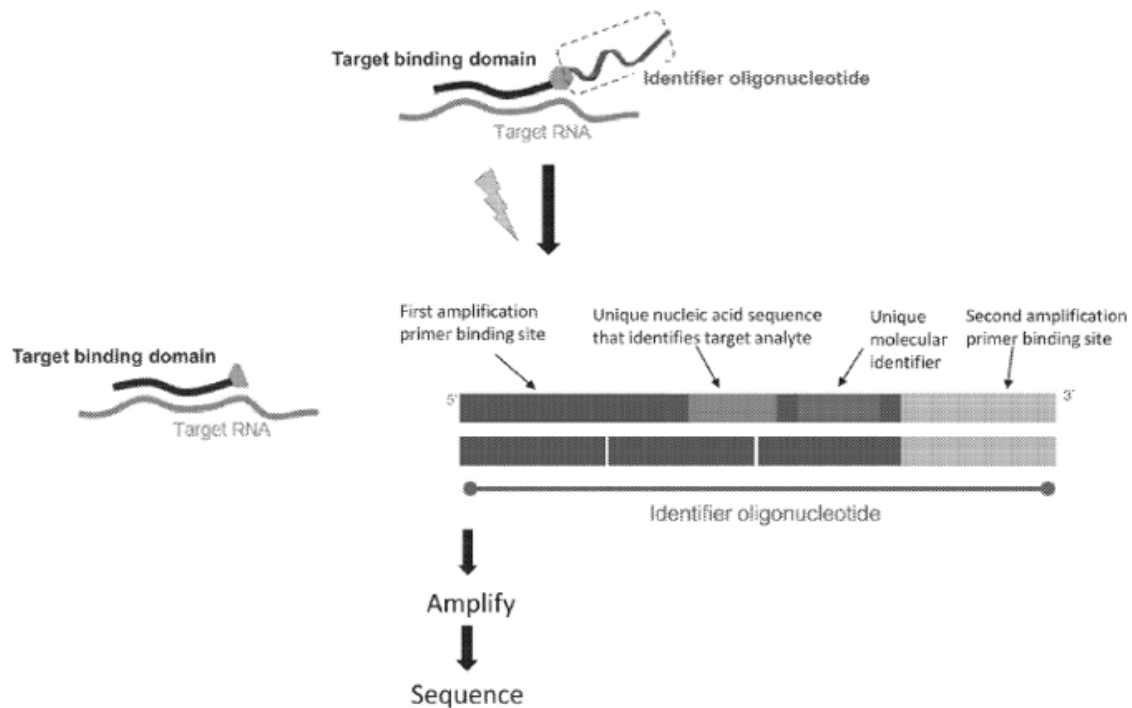


Figure 11 “shows a schematic of a preferred aspect of a direct PCR method” of the ’689 patent. *Id.* at 32:27–51. After the probe hybridizes and the identifier nucleotide is cleaved, amplification of the identifier oligonucleotide occurs, which is initiated by binding of amplification primers at the 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 32:50–51. The ’689 patent refers to this process as “spatially detecting” a target analyte. *See, e.g., id.* at 30:51–31:5.

*E. Illustrative Claims*

Claims 1 and 16 are independent. Representative claim 1 is reproduced below:

1. A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising:

a) contacting the tissue sample with a plurality of nucleic acid probes, wherein each of the nucleic acid probes comprise a target binding domain that binds to the at least one target analyte, wherein the tissue sample [has been] is treated to facilitate binding of the nucleic acid probes to the target analyte;

b) collecting the nucleic acid probes, or portions thereof, bound to the at least one target analyte in a first location of the tissue sample under conditions that release the nucleic acid probes, or portions thereof, from the first location of the tissue sample;

c) collecting the nucleic acid probes, or portions thereof, bound to the at least one target analyte in a second location of the tissue sample under conditions that release the nucleic acid probes, or portions thereof, from the second location of the tissue sample;

d) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the first location of the tissue sample into each of the nucleic acid probes, or portions thereof, collected in step (b), thereby forming a first plurality of extension products that comprise the nucleic acid probes, or portions thereof, collected in step (b) and the at least one nucleic acid sequence that identifies the first location of the tissue sample;

e) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the second location of the tissue sample into each of the nucleic acid probes, or portions thereof, collected in step (c), thereby forming a second plurality extension products that comprise the nucleic acid probes, or portions thereof, collected in step (c) and

the at least one nucleic acid sequence that identifies the second location of the tissue sample; and

f) identifying the first plurality of extension products and the second plurality of extension products by sequencing the first plurality of extension products and the second plurality of extension products, thereby spatially detecting the at least one target analyte in the first location of the tissue sample and the second location of the tissue sample.

Ex. 1001, 145:51–147:11.

Whereas claim 1 recites contacting the tissue sample with “a plurality of nucleic acid probes”, claim 16 recites using a “first” and a “second plurality of probes” and further adds a ligation step in which the first and second probes are ligated to form “ligated probes,” which are then collected. 147:54–148:47. The remainder of the claims depend from either claim 1 or 16 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 147:13–150:18.

#### *F. Prior Art and Asserted Grounds*

Petitioner asserts that claims 1–30 would have been unpatentable on the following grounds:

| <b>Claim(s) Challenged</b> | <b>35 U.S.C. §<sup>2</sup></b> | <b>Reference(s)/Basis</b> |
|----------------------------|--------------------------------|---------------------------|
| 1–8, 11–23, 26–30          | 102                            | So-456 <sup>3</sup>       |
| 1–30                       | 103                            | So-456                    |

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<sup>2</sup> 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 ’689 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.

<sup>3</sup> WO 2017/019456, published February 2, 2017 (Ex. 1005, “So-456”).

| Claim(s) Challenged | 35 U.S.C. § <sup>2</sup> | Reference(s)/Basis         |
|---------------------|--------------------------|----------------------------|
| 9, 10, 24, 25       | 103                      | So-456, Stahl <sup>4</sup> |
| 1–30                | 102                      | Chell <sup>5</sup>         |

In support of its contentions, Petitioner relies on the Declaration of Paul T. Spellman, Ph.D. (Ex., 1002).

## 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 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

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<sup>4</sup> Stahl et al., *Visualization and analysis of gene expression in tissue selections by spatial transcriptomics*, SCIENCE 353(6294):78–82, July 1, 2016 (Ex. 1016, “Stahl”).

<sup>5</sup> WO 2021/133849, published July 1, 2021 (Ex. 1006, “Chell”).

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).

A patent claim is unpatentable under 35 U.S.C. § 103 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.<sup>6</sup> *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

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<sup>6</sup> Patent Owner does not presently assert objective indicia supporting non-obviousness of the challenged claims. *See generally* Prelim. Resp.; PO PI Sur-reply.

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 ’689 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. 14 (citing Ex. 1002 ¶¶ 24–25).

For the purposes of its Preliminary Response, Patent Owner does not provide its own proposed level of skill. Prelim. Resp. 10. For purposes of this Decision, we apply Petitioner’s unchallenged definition as it is consistent with the cited prior art and disclosure of the ’689 patent.

### *C. Claim Construction*

Petitioner provides no claim construction for any term, but asks that we apply Patent Owner’s interpretations of the ’689’s patent claims from the concurrent litigation. Pet. 14–15. Petitioner alleges “[i]n concurrent litigation, NanoString alleged that these collecting steps encompass diffusion and capture of *whole* ligation products generated from ligating the primary probe pairs across the *whole* tissue sample, all at the same time.” *Id.* at 20 (citing Ex. 1020, 22–27, 53–54; Ex. 1008, 19–20; Ex. 1002 ¶¶ 116, 132). Petitioner provides Patent Owner’s infringement contentions (Ex. 1020) and Answer and Counterclaim (Ex. 1012) as evidence of Patent Owner’s interpretations. Patent Owner states that it “does not dispute that the ‘collecting’ steps in claims 1 and 16 include the capture of entire probes” and that no claim construction order has been entered by the district court in the concurrent litigation. Prelim. Resp. 14.

For purposes of institution, we discern that we must interpret “collecting the nucleic acid probes,” which we do below in relation to Petitioner’s allegations of anticipation by So-456. Any final written decision

entered in this case may include a final claim construction based on the full trial record that differs from this preliminary construction, or from any discussion of claim scope provided in our analysis below.

*D. Anticipation by So-456*

Petitioner alleges that So-456 anticipates claims 1–8, 11–23, and 26–30. Pet. 15–18.

*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 tissue 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:

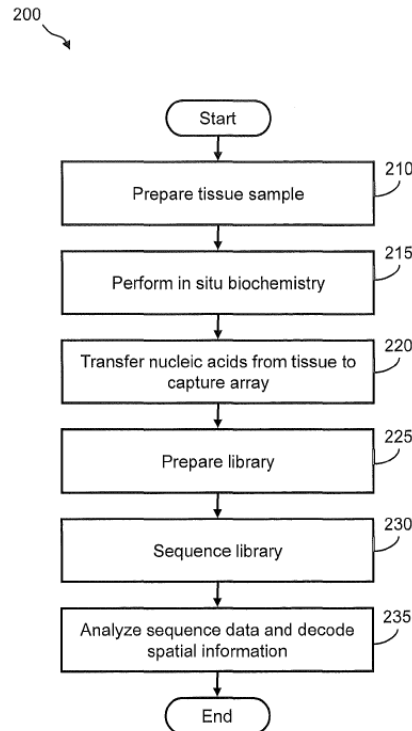


Figure 2 “illustrates a flow diagram of an exemplary embodiment of a method of spatial detection and analysis of nucleic acid in a tissue sample.”  
*Id.* ¶ 12.

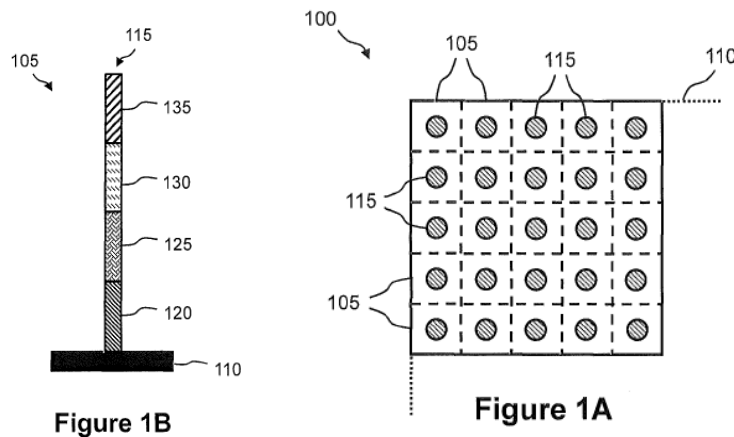
So-456 discloses encoding information identifying the spatial origin of a nucleic acid in a tissue sample during the process of preparing the nucleic acid for sequencing:

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, which 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 by in situ amplification of target nucleic acids.

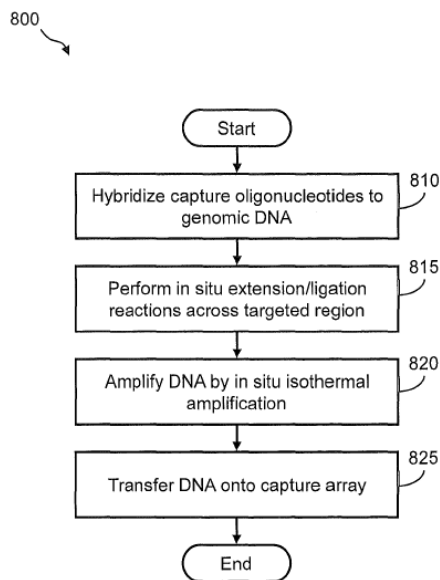


**Figure 8**

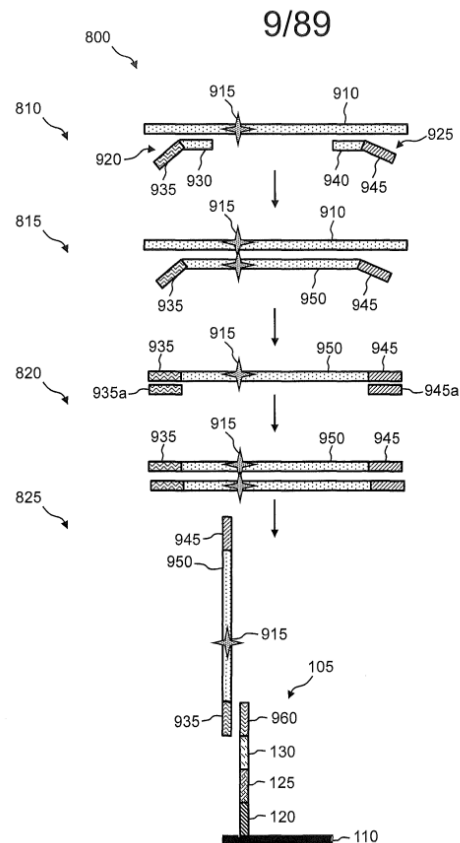


**Figure 9**

Figure 8, reproduced above, is a flow diagram of the method of creation and capture of DNA amplicons generated 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 a 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.” *Id.* 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 captured 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 anticipates claims 1–8, 11–23, and 26–30. Pet. 15–18. Patent Owner disagrees and alleges that So-456 does not teach four limitations recited in the challenged independent claims. Prelim. Resp. 15–36. Patent Owner focuses its arguments on independent claims 1 and 16. *Id.* As Patent Owner does, we focus our discussion below on the limitations of claims 1 and 16 that Patent Owner alleges So-456 does not teach.

### *a) Collecting the Nucleic Acid Probes*

#### *(1) Allegations of the Parties*

Patent Owner argues that So-456 does not teach “collecting the nucleic acid probes” of claim elements b) or c) of claim 1 (requiring “collecting the nucleic acid probes, or portions thereof, bound to the at least

one target analyte in a first/second location”<sup>7</sup>) or claim elements c) or d) of claim 16 (requiring “collecting the nucleic acid probes, or portions thereof, bound to the at least one target analyte in a first/second location”). *See* Prelim. Resp. 16–19 (citing similar language of claim 16). Patent Owner argues that So-456 instead teaches *amplification* of probes, and capturing of the amplified products, the “genomic amplicons.” *Id.* at 17–18.

We next turn to Petitioner’s allegations regarding how So-456 discloses “collecting the nucleic acid probes.” Petitioner provides annotated versions of Figures 9 and 1A, reproduced below:

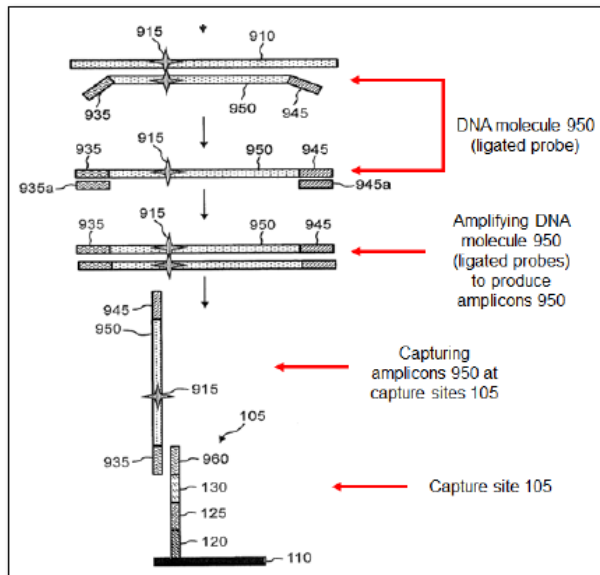


**Figure 9**

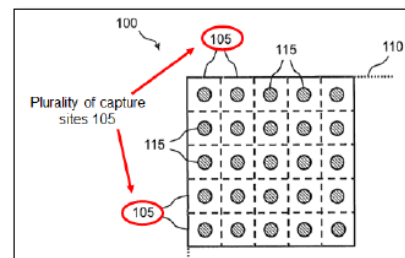


**Figure 1A**

Figure 9 illustrates an exemplary embodiment of the method of creation of and capture of DNA amplicons generated by in situ amplification of target nucleic acids. Ex. 1005 ¶ 19. Figure 1A “illustrates a plan view of an

<sup>7</sup> Claim elements b and c, and d and e are grouped in this discussion for brevity as the only different terms are “first” and “second.”

exemplary embodiment of a capture array for capture of nucleic acid in a tissue sample.” *Id.* ¶ 9.

Petitioner alleges that So-456’s method discloses amplification of the ligated probes (950) to produce “unbound amplified ligated probes” or “amplicons” (also 950), which are free from the target DNA molecules.

Pet. 20. These amplicons are then “captured” on a capture array by passive diffusion where they bind to a capture site, 105, as shown in Figure 1A. *Id.* (citing Ex. 1005 ¶¶ 182, 215; Figures 2, 8, 9; Ex. 1002 ¶¶ 134, 135).

Petitioner alleges the capture site “comprises immobilized array probes (‘capture probes’ 115) containing a spatial barcode (‘spatial address region’ 130) and a ‘capture region’ (135 or 960) that hybridizes a complementary region on the ligated probes (‘universal capture region’ 935).” *Id.* at 20–21 (citing Ex. 1005 ¶¶ 141, 182, 183; Ex. 1002 ¶¶ 135–137). Petitioner alleges So-456’s workflow “collects *whole* ligated primary probes from the *whole* tissue sample at the same time” as it is performed in multiple locations on the tissue sample at multiple capture sites on the array. *Id.* at 22 (citing Ex. 1005 ¶¶ 141, 183, Figures 1A, 9; Ex. 1002 ¶¶ 136, 137). *See also* Pet. 29, alleging “So-456 teaches claim 1’s collecting steps for the reasons discussed above for claim 16.”

## (2) Analysis

After review of the evidence of record, we conclude that it is necessary to interpret “collecting the nucleic acid/ligated probes” for purposes of institution. Despite its importance to this issue, neither party has construed “collecting the nucleic acid/ligated probes” or “probe,” though Petitioner’s declarant, Dr. Spellman, opines that the ’689 patent Specification discloses two types of probes, 1) “probes” that “are *primary* probes that contain a target-binding domain and hybridize to a target analyte

in the sample (an ‘on-analyte’ hybridization)” and 2) “nucleic acid probes,” which are “pairs of *secondary* probes that do not contain a target-binding domain and are never bound to the target analyte.” Ex. 1002 ¶¶ 56, 57 (emphasis original). Dr. Spellman provides the following Table 1, reproduced below, reflecting the types of probes disclosed in the ’689 patent.

| TABLE 1: Oligonucleotides disclosed in the 689 patent |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oligonucleotide                                       | Disclosure in the specification (excluding the claims)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| “Probes”                                              | Primary probes having a target-binding domain that binds to the target analytes in a tissue sample (on-analyte binding)<br><br>“The present disclosure provides <i>probes</i> comprising a <i>target binding domain</i> and an <i>identifier oligonucleotide</i> .” EX1001, 37:14-16 (emphasis added).                                                                                                                                                                                                                                                                                                |
| “Nucleic acid probes”                                 | Secondary probes: pairs of oligonucleotides that hybridize to the identifier oligonucleotide cleaved off from the “probes” (off-analyte binding)<br><br>“[H]ybridizing to the released identifier oligonucleotide a <i>first nucleic acid probe</i> and a <i>second nucleic acid probe</i> , wherein the first nucleic acid probe comprises a nucleic acid complementary to a portion of the identifier oligonucleotide . . . and wherein the second nucleic acid probe comprises a nucleic acid complementary to a portion of the identifier oligonucleotide....” EX1001, 5:44-6:8 (emphasis added). |

*Id.* ¶ 58. Table 1 above, from Dr. Spellman’s declaration, describes the types of probes disclosed in the ’689 patent. However, Dr. Spellman notes that his classification of the disclosed probes *excludes how the probes are described in the claims*. *Id.*

To interpret “collecting the nucleic acid probes,” we turn first to the words of claim 1 itself, to interpret “nucleic acid probe” in claim 1. *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 “nucleic acid probe,” with the relevant text shown in *italics* below.

a) contacting the tissue sample with a plurality of nucleic acid probes, *wherein each of the nucleic acid probes comprise a target binding domain that binds to the at least one target analyte*, wherein the tissue sample [has been] is treated to facilitate binding of the nucleic acid probes to the target analyte

b/c) *collecting the nucleic acid probes*, or portions thereof, *bound to the at least one target analyte* in a first/second location of the tissue sample *under conditions that release the nucleic acid probes*, or portions thereof, from the first/second location of the tissue sample

d/e) performing an extension reaction that *incorporates at least one nucleic acid sequence that identifies the first/second location of the tissue sample into each of the nucleic acid probes*, or portions thereof, collected in step (b), thereby forming a first plurality of extension products that comprise the nucleic acid probes, or portions thereof, collected in step (b) and the at least one nucleic acid sequence that identifies the first/second location of the tissue sample

Ex. 1001, 145:51–147:11 (emphasis added).

Thus, according to claim 1, the “nucleic acid probe” must 1) comprise a target binding domain that binds to the at least one target analyte, 2) be bound to the at least one target analyte; 3) be released in whole or as a portion, and 4) have a location-identifying nucleic acid sequence incorporated into it through an extension reaction. Steps a), b), and c) occur in relation to the target analyte, while steps d) and e) occur after the probe is

collected. *Id.* Claim 16 adds that the probes must be ligated to each other after binding. Ex. 1001, 148:5–10.

Turning to the Specification, we agree with Dr. Spellman that the characterization of “nucleic acid probe” in the ’689 patent is at odds with the language of claims 1 and 16. *See, e.g.*, Ex. 1002 ¶ 77. In the disclosure, “nucleic acid probes” bind to cleaved portions from the “probe” (what Dr. Spellman calls the “primary probe”) that contain the identifier oligonucleotide, not the target binding domain, which is described as being bound by “probes” rather than “nucleic acid probes.” *Compare* Ex. 1001, 37:14–16 (“The present disclosure provides *probes* comprising a target binding domain and an identifier oligonucleotide”) with 5:54–56 (“hybridizing to the released identifier oligonucleotide a *first nucleic acid probe* and a *second nucleic acid probe* ...”) (emphases added).

Furthermore, all instances of “collecting” and “collected” in the Specification relating to nucleic acids refer to the “released identifier oligonucleotide” or the “collected identifier oligonucleotide” rather than the target binding domain itself. *See, e.g.*, Ex. 1001, regarding “collecting” 2:11; 4:33; 8:27; 22:27; 35:52; and regarding “collected” 13:4; 17:25; 22:45; *see also id.* at 17:17–21 (“identifier oligonucleotides are collected only f[rom] *probes that are bound to targets within that location*, thereby permitting detection of the identities and quantities of the targets (proteins and/or nucleic acids) located only within that location.”). Thus, the Specification informs us that “collecting the nucleic acid probes” refers to collecting identifier nucleotides released after application of a force (e.g., conditions that release the nucleic acid probes) from the location of the sample, for example by aspirating solution in which the free-floating oligonucleotide is found. *See, e.g.*, Ex. 1001, 39:33–39 (disclosing that a

“proximal solution may be collected by aspirating, e.g., using a pipette, a capillary tube, a microarray pin, a flow cell comprising holes, or another suitable aspirating system”). After collection, the recited extension reaction is then performed, whereby the “at least one nucleic acid sequence that identifies the first/second location of the tissue sample into each of the nucleic acid probes” is incorporated into the extension product. Ex. 1001, 145:51–147:11.

Turning to other intrinsic evidence, the prosecution history does not have pertinent evidence regarding claim interpretation of *collecting* nucleic acid probes. *See generally*, Ex. 1004.

With this information in hand, we interpret “collecting the nucleic acid probes.” “[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 (Fed. Cir. 1998).

Consistent with the claim language when read in light of the Specification, we interpret a “nucleic acid probe,” consistent with its usage in claims 1 and 16, as an oligonucleotide comprising a target binding domain that binds to one or more target analytes, and is modified after collection to comprise a location-identifying nucleic acid sequence for use in identifying the location of the target analyte.

We further interpret “collecting the nucleic acid probes” to mean “releasing all or a portion of the nucleic acid probe bound to the at least one target analyte through application of a force followed by retrieval of the released probe or portion of the probe.”

The question then becomes whether So-465, which teaches replication of a probe that was bound and then at least partially released to make genomic amplicons, followed by collection of those genomic amplicons, anticipates collection of probes as recited in claims 1 and 16. On this record, we do not see sufficient evidence that the genomic amplicons disclosed in So-456 that Petitioner identifies as “captured” were ever “bound to the analyte” in part or in whole as required by the claim language, but rather were amplified in situ from the probe or partial probe that was released. Ex. 1005 ¶¶ 181–183. In particular, the process of So-456 differs from the ’689 patent claims in that the extension reaction to incorporate the tissue-identifying nucleic acid sequence in So-465 occurs after the identifier nucleotide is cleaved from the tissue sample. “Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference.” *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009). Petitioner has not demonstrated that So-456 teaches this claim limitation or otherwise demonstrates that this limitation would have been inherent in the disclosure of So-456 for claims 1 and 16. For these reasons, on this record we determine that Petitioner has not shown a reasonable likelihood that So-456 anticipates either of independent claims 1 or 16.

In sum, based on the record before us, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that So-456 anticipates claims 1–8, 11–23, and 26–30. Nevertheless, the Board, in a decision to institute under 35 U.S.C. § 314(b), may not institute

review on fewer than all claims challenged in the petition. *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018). In addition, if the Board institutes trial, it will institute on all grounds in the petition. *See* 37 C.F.R.

§ 42.108(a) (“When instituting . . . 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.”); *see also PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require “a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition”).

For the reasons explained below, we determine that Petitioner has met its burden under 35 U.S.C. § 314(a) as to its challenge of at least one claim of the ’689 patent on other grounds. Thus, we institute *inter partes* review as to all claims challenged in the Petition, and on all grounds presented, pursuant to *SAS* and 37 C.F.R. § 42.108(a). Because we institute on other grounds, we provide the following additional observations below regarding our evaluation of the evidence of record on the remaining three disputed limitations in claims 1 and 16 for use by the parties in this proceeding.

*b) Treated Tissue Sample*

*(1) Allegations of the Parties*

Patent Owner alleges So-456 does not disclose the claim element “wherein the tissue sample is treated to facilitate binding of the nucleic acid probes to the target analyte” as recited in claims 1 and 16. Prelim. Resp. 20. Patent Owner argues that So-456 discloses only sectioning, staining, and fixing a tissue sample on a slide, but that none of these facilitate binding of nucleic acid probes. *Id.* at 21 (citing Ex. 1005 ¶ 125). Rather, Patent Owner argues that So-456 “describes introducing probes without any treatment to the tissue sample.” *Id.* Patent Owner argues that, without such treatment, it

is unclear how a nucleic acid probe would bind paraffin-fixed tissue and contrasts the pre-probe tissue treatment disclosed in Chell, which Patent Owner argues constitutes “treating a tissue sample to facilitate binding of nucleic acid probes to a target analyte.” *Id.* at 21–22.

We next turn to Petitioner’s allegations regarding how So-456 discloses “wherein the tissue sample is treated to facilitate binding of the nucleic acid probes to the target analyte.” Petitioner alleges that So-465 teaches treating the tissue sample because it “discloses that the ‘*tissue sample is prepared for analysis*’ and that ‘*in situ biochemistry is performed on the tissue section to facilitate subsequent manipulation of a nucleic acid in the sample.*’” Pet. 18 (citing Ex. 1005 ¶¶ 152–153; Ex. 1002 ¶¶ 125–127) (emphasis in original). Petitioner points to Figures 2 and 8 as evidence of the in situ biochemistry and hybridizing capture oligonucleotides to genomic DNA. *Id.* at 18–19 (citing Ex. 1005, Figures 2, 8, 9, ¶¶ 153, 178, 182; Ex. 1002 ¶¶ 125–127). In support, Dr. Spellman opines consistent with Petitioner’s ipso facto position, that the tissue in So-456 must have been prepared to allow binding of the nucleic acid because Figure 8 depicts binding of oligonucleotides to genomic DNA. Ex. 1005 ¶¶ 126–127 (stating that

Because the capture oligonucleotides hybridized to the target analytes and were processed according to the subsequent steps, So-456’s method treated the tissue sample to facilitate binding of the first and second plurality of capture oligonucleotides (i.e., nucleic acid probes of the claim) to the target DNA molecules (i.e., target analytes)).

## (2) Analysis

After review of the evidence of record, we conclude that the parties have not sufficiently addressed the meaning of “wherein the tissue sample is

treated to facilitate binding of the nucleic acid probes to the target analyte” in claims 1 and 16. We encourage the parties to address the disclosures of the ’689 patent with respect to this term as well as the knowledge of an ordinarily skilled artisan at the time of the invention regarding this process.

*c) Required Extension Reaction Steps*

Patent Owner alleges So-456 does not disclose the claim element “performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the first/second location of the tissue sample into each of the nucleic acid probes, or portions thereof” (“performing an extension reaction”) as recited in claims 1 and 16. Prelim. Resp. 23–33.

*(1) Allegations of the Parties*

Patent Owner argues that Petitioner’s evidence for this limitation is based on inherency only, and that Petitioner does not “demonstrate that the protocols disclosed in So-456 *would necessarily* result in incorporating the spatial address region via an extension reaction.” *Id.* at 35 (emphasis original).

Petitioner relies on Figure 9 as evidence to show that because the ligated probes that are captured on an array are “not yet tagged with a spatial barcode and do not include functional sequences (i.e., a pair of SBS primer-binding sites) necessary for performing sequencing-by-synthesis (SBS) in subsequent steps,” the ligated probe would necessarily be extended *in both directions*, which bi-directional extension would result in the incorporation of the “spatial barcode and sequencing primer-binding sites.” Pet. 25–26. Petitioner argues that the extension reaction is inherently bi-directional because So-456 did not teach methods to *prevent* the extension from occurring and all the components needed for bi-directional extension are present. *Id.*

(2) *Analysis*

After review of the evidence of record, we conclude that, on this record, Petitioner does not show sufficient evidence of inherently bi-directional extension. In particular, we do not find that one of ordinary skill in the art would have read So-456 to disclose an extension reaction replicating the spatial barcode due to the lack of disclosure on this issue. We encourage the parties to further develop this issue at trial.

d) *Forming ligated probes*

Patent Owner alleges So-456 does not disclose the claim element “forming a first/second plurality of extension products that comprise the ligated probes” (“forming ligated probes”) as recited in claim 16. Prelim. Resp. 33–37.

(1) *Allegations of the Parties*

Patent Owner argues that So-456 does not disclose “forming ligated probes” because, rather than ligating two nucleic acid probes to form a ligated probe, So-456 uses an “extension/ligation reaction” between non-adjacent probes. *Id.* at 33. Patent Owner argues the probes cannot be ligated by a nick ligation process as disclosed in the patent because they are not adjacent, but rather ligate the extension products together *after* the extension reaction occurs. *Id.* at 35–36.

Petitioner, through Dr. Spellman, alleges that So-456 discloses this term because “So teaches that ‘an extension/*ligation* reaction is performed in situ between the flanking capture oligonucleotides 920 and 925 [i.e., the primary nucleic acid probe pairs] across the region of interest,’ which forms ligated probes (‘DNA molecule 950’), as claimed.” Pet. 19 (citing Ex. 1005 ¶ 182, Figures 8, 9; Ex. 1002 ¶¶ 128–130).

(2) *Analysis*

After review of the evidence of record, we conclude that the parties have not sufficiently addressed the meaning of “ligating the probes” in claim 16. We encourage the parties to address the disclosures of the ’689 patent with respect to this term as well as the knowledge of an ordinarily skilled artisan at the time of the invention regarding this process.

*E. Obviousness over So-456*

*1. Allegations of the Parties*

Petitioner alleges that, to the extent So-456 does not anticipate claims 1–8, 11–23, and 26–30, So-456 renders all of claims 1–30 obvious. Pet. 39–48 (citing, e.g., Ex. 1002 ¶¶ 218–254). Petitioner argues that an ordinarily skilled artisan would have been motivated to make a sequencing library because the goal of So-456 was to “create a sequencing library of sequences that are (i) tagged with spatial barcodes and (ii) include the necessary pair of SBS primer-binding sites for [next generation sequencing] NGS.” *Id.* at 42. Petitioner argues the artisan would have found it obvious to include the “performing an extension reaction” limitation because using such a reaction to extend probes was “a well-known, obvious, and routine technique for incorporating the spatial barcode (and necessary second sequencing primer) into the resulting extension reaction products to produce the desired finished sequencing library.” *Id.* Petitioner cites evidence of commercially available primer sequences and other supporting components (*id.* at 42–43) and argues that the artisan would have reasonably expected to succeed in making the claimed subject matter because of the “ample guidance and direction” including working examples in the art. *Id.* at 43–45. Petitioner incorporates its allegations regarding anticipation by So-456 of the dependent claims and argues that the ordinarily skilled artisan would have been motivated to

include unique molecular identifiers in the capture probes of So-456, and would have had reasonable success in doing so. *Id.* at 46–48.

Patent Owner disagrees and argues that the claims are not obvious for the same reasons they are not anticipated as addressed above. Prelim. Resp. 15–36 (arguing issues together). The sole argument Patent Owner articulates separately with regard to non-obviousness regards the “performing an extension reaction” claim limitation. *Id.* at 30–33. Patent Owner argues that the proposed extension reaction from the direction of the capture probe would not incorporate a spatial barcode because none exists at that location to incorporate. *Id.* at 31–32. Patent Owner argues that despite the technique for extension being routine in the art, extension of the probe is not necessary or obvious because “an extension of the capture probe would incorporate the target analyte sequence as well as the necessary second SBS primer-binding site from the *captured* probe onto the *capture* probe.” *Id.* at 32 (emphasis original). Because such uni-directional extension would create a molecule with both primers, Patent Owner argues, there would be no motivation to find a different method, nor is it inherent that such extension happens. *Id.* at 32–33.

## 2. Analysis

After reviewing the record of evidence, we find Petitioner’s case for obviousness is stronger than its case for anticipation from a technical perspective due to the high level of skill in the art that could have assisted an ordinary artisan in understanding how to bridge the gaps between one or more disclosures of So-456 and the challenged claims. For instance, to the extent So-456 did not disclose “wherein the tissue sample is treated to facilitate binding of the nucleic acid probes to the target analyte” as recited in claims 1 and 16, we agree with Petitioner that an ordinarily skilled artisan

would have known how to prepare tissue for in situ histochemistry. *See* Ex. 1003 ¶ 24 (Dr. Spellman’s proposed definition of a person of ordinary skill in the art, unopposed by Patent Owner, stating that the artisan “would have possessed a strong understanding 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 section”).

However, Petitioner’s allegations regarding the obviousness of independent claims 1 and 16 do not address the deficiency discussed above with regard to the limitation “collecting the nucleic acid probes.” *See* Section II.D.2.a. Specifically, Petitioner does not allege or provide evidence to support that the skilled artisan would have found it obvious based on the teachings of So-456 to collect the cleaved identifier oligonucleotides rather than the genomic amplicons as alleged. In addition, we share Patent Owner’s view that Petitioner, on this record, does not sufficiently show a motivation for the ordinarily skilled artisan to have included a spatial barcode in the capture probes of So-456. We suggest the parties further address these issues at trial.

#### *F. Obviousness over So-456 and Stahl*

Petitioner alleges claims 9, 10, 24, and 25 are obvious over So-456 and Stahl. Pet. 49–52.

##### *1. Stahl (Ex. 1016)*

Stahl is a journal article entitled “*Visualization and analysis of gene expression in tissue sections by spatial transcriptomics*.” 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 capture probes containing spatial barcodes and UMIs to allow both 1) identification of corresponding surface probes on the solid substrate (e.g., tissue sample), and 2) identification of duplicate post-amplification molecules. *Id.*, Figure 2A.

## *2. Disputed Issues*

Petitioner alleges claims 9, 10, 24, and 25 are obvious over So-456 and Stahl. Pet. 49–52. In particular, Petitioner alleges that the combined disclosures of So-456 and Stahl teach or suggest modifying So-456’s capture probe to include a UMI as disclosed in Stahl’s capture probes. *Id.* at 49.

Patent Owner disagrees and alleges that, as discussed above, So-456 does not teach four limitations recited in the challenged independent claims, and Petitioner’s obviousness case does not rely on Stahl to provide the missing claim elements. Prelim. Resp. 5.

## *3. Analysis*

Challenged claims 9, 10, 24, and 25 depend from independent claims 1 or 16. Petitioner relies on the same allegations it made regarding anticipation and obviousness over So-456 for the disclosure of all limitations of independent claims 1 and 16. Pet. 49. Petitioner does not rely on Stahl to cure the deficiencies for any of the limitations we found lacking in the prior challenges. *See* II.D., II.E. For the same reasons discussed in the prior challenges, on the current record, Petitioner has not shown a reasonable likelihood of success in showing obviousness of claims 9, 10, 24, and 25.

### *G. Anticipation by Chell*

#### *1. Chell (Ex. 1006)*

Chell is a published patent application assigned to Petitioner. Ex. 1006, codes (10), (71). Chell discloses “methods of detecting an analyte

of interest to interrogate spatial gene expression in a sample using RNA-templated ligation.” *Id.*, Abstract. Chell discloses:

a method for determining a location of an analyte in a biological sample including: (a) providing the biological sample on an array including a plurality of capture probes, where a capture probe of the plurality includes: (i) a spatial barcode and (ii) a capture domain; (b) contacting a first probe and a second probe with the biological sample, where the first probe and the second probe each include one or more sequences that are substantially complementary to sequences of the analyte, and where the second probe includes a capture probe capture domain; (c) hybridizing the first probe and the second probe to the analyte; (d) generating a ligation product by ligating the first probe and the second probe; (e) releasing the ligated product from the analyte; (f) hybridizing the ligation product to the capture domain; and (g) determining (i) all or a part of the sequence of the ligation product bound to the capture domain, or a complement thereof, and (ii) all or a part of the sequence of the spatial barcode, or a complement thereof, and using the determined sequence of (i) and (ii) to identify the location of the analyte in the biological sample.

*Id.* at 2:9–22. *See also* Figure 13 (workflow diagram).

## 2. *Disputed Issues*

Petitioner alleges that Chell discloses all limitations of challenged claims 1–30. Pet. 52–75. Petitioner further alleges that Chell, which was filed and published before the ’689 patent was filed, is intervening prior art because the priority application for the ’689 patent, the 487 application, does not provide written descriptive support for the full scope of the claims. *Id.* at 52. Patent Owner, for purposes of institution, does not dispute that Chell anticipates claims 1–30, but argues that Chell cannot be prior art because the priority application provides written description support for the full scope of

the claims. Prelim. Resp. 36–42. Because Chell’s status as prior art is a threshold issue, we address this first.

### 3. *Allegations of the Parties*

Petitioner alleges that the 487 application does not provide written descriptive support for the claim limitations 1) collecting whole probes; and 2) hybridizing pairs of primary nucleic acid probes to target nucleic acids in a sample followed by ligation of the same probe pairs, prior to release or collection. Pet. 54–55. Petitioner alleges that because the 487 application does not contain this written description support, the claims are only entitled to the filing date of the application leading to the ’689 patent, September 16, 2021, which would render Chell, with a July 1, 2021, publication date, prior art to the ’689 patent. *Id.* at 5. Petitioner argues that the 487 application only describes collecting portions of probes that are cleaved off by force (e.g., application of UV light) and not release of whole probes. *Id.* at 53–55 (citing Ex. 1009, e.g., ¶¶ 5–7, 24–27, 174–177; Ex. 1002 ¶¶ 278–286). Petitioner further argues that the challenged claims recite “a particular arrangement and usage of primary (analyte-binding) probes” taking place on the target analyte before release or collection, which differs from the 487 application’s disclosure of “distinct on-analyte and off-analyte steps.” *Id.* at 55–56 (citing Ex. 1009, e.g., ¶¶ 5–7, 24–27, 231–232; Ex. 1002 ¶¶ 278–292). Petitioner argues that the 487 application does not describe the “on-analyte” ligation recited in the claims. *Id.*

Patent Owner disagrees and argues that the 487 application discloses embodiments wherein “the entire ‘intact probe’ is collected.” Prelim. Resp. 38 (citing Ex. 1009 ¶ 252). Patent Owner argues that the disclosure contemplates both whole and partial probe use. *Id.* at 39 (citing Ex. 1009 ¶ 261). Patent Owner further argues that one of ordinary skill in the art

would have understood the 487 application to disclose the claimed hybridization and ligation methods. *Id.* at 40–42.

On reply, Petitioner argues that the cited paragraphs of the 487 application, paragraphs 252 and 261, do not disclose collecting nucleic acids that are bound to the target analyte for extension through the recited extension reaction, but rather describe a “negative purification” process whereby whole probes are removed to reduce background noise in the nucleic acid detection process. Pet. PI Reply, 1–2. Petitioner cites additional disclosures in the 487 application as support for its interpretation. *Id.* at 2–3.

In response, Patent Owner argues that Petitioner concedes that the 487 application discloses “intact probes” for use in the methods of the disclosure, which adequately describes the probes sufficiently to support its priority claim. PO Prelim. Reply, 1–2. Patent Owner further argues that Petitioner fails to meet its burden to explain why this disclosure would not describe using intact probes sufficiently to enable one of ordinary skill in the art to understand the full scope of the claims. *Id.* at 3.

#### 4. Analysis

As discussed above, Petitioner has asked that we apply Patent Owner’s interpretations of the ’689’s patent claims from the concurrent litigation, in which Patent Owner alleges that the “collection” step encompasses diffusion and capture of whole ligation products generated from ligating the primary probe pairs across the whole tissue sample, all at the same time, which would include capture of entire probes. *See supra*, II.C.

On the record before us, solely for purposes of institution, we find that the 487 application does not describe the use of whole/intact probes that

are collected and extended as recited in the challenged claims. Rather, paragraphs 252 and 261 of the 487 application describe whole/intact probes floating in the in situ histochemistry milieu, and not bound to target analytes as the claims require. Ex. 1009 ¶¶ 252, 261. We conclude that, on this record, the disclosure of the 487 application describes whole probes only in the context of removing unbound whole probes to reduce signal noise. *Id.* As described above, all references to “collecting probes” refer only to cleaved off identifier oligonucleotides, not release of entire probes. Thus, for purposes of institution, we find that the 487 application does not provide written description support for the full scope of the claims, and that Chell is prior art. We invite the parties to further develop this issue as well as the issue of whether the 487 application provides written description support for “on-analyte” ligation as recited in the claims during trial. We now turn to the question of whether Chell anticipates the challenged claims.

#### 5. *Anticipation*

Petitioner alleges that Chell discloses all limitations of challenged claims 1–30. Pet. 52–75. Patent Owner, for purposes of institution, does proffer any evidence to support its stated argument that Chell does not anticipate claims 1–30. *See, generally*, Prelim. Resp.

We have reviewed the evidence of record and determine, for the purposes of institution, that Petitioner has demonstrated that there is a reasonable likelihood that at least one of the challenged claims is unpatentable. In particular, we are persuaded by the evidence provided by Dr. Spellman regarding Chell’s disclosure of each claim limitation of claims 1 and 16. *See* Ex. 1002 ¶¶ 294–349; Ex. 1006, Figures 6, 13. Nevertheless, we recognize that the issues in dispute are highly fact-intensive and implicate genuine issues of fact more appropriately resolved on a fully

developed record. In the absence of any argument on this ground from Patent Owner, we will evaluate this ground on the record that is developed during trial.

### 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 '689 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. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting that “there is a significant difference between a petitioner’s burden to establish a ‘reasonable likelihood of success’ at institution, and actually proving invalidity by a preponderance of the evidence at trial”). Any final decision in this proceeding will be based on the full trial record.

The Board will deem forfeited any issue not raised by Patent Owner in a timely response to the Petition, or as permitted in another manner during trial, even if asserted in the Preliminary Response or discussed in this Decision.

Nothing in this Decision authorizes Petitioner, in a manner not otherwise permitted by the Board's rules, to supplement the information pertaining to any ground advanced in the Petition.

#### 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.

IPR2023-01298  
Patent 11,377,689 B2

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