

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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Case IPR2023-01298  
U.S. Patent No. 11,377,689

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**PATENT OWNER'S PRELIMINARY RESPONSE TO PETITION FOR  
*INTER PARTES* REVIEW OF U.S. PATENT NO. 11,377,689**

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**EXHIBIT LIST**

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                 |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2001               | Gullberg, Mats, <i>et al.</i> “Cytokine detection by antibody-based proximity ligation,” Proceedings of the National Academy of Sciences 101.22, 8420-8424 (2004). |

## I. INTRODUCTION

Patent Owner NanoString Technologies, Inc. (“NanoString” or “Patent Owner”) submits this Preliminary Response to Petitioner 10X Genomics, Inc.’s (“10X” or “Petitioner”) Petition for *Inter Partes* Review of U.S. Patent No. 11,377,689 (“Petition”). For the reasons stated below, the Board should not institute review.

NanoString is a pioneer in the field of spatial biology. As a respected, leading innovator of translational tools, NanoString has developed and brought to market breakthrough technologies that enable scientists across the globe to envision molecular interactions in three dimensions. NanoString’s spatial profiling patents and products are the first of their kind – they uniquely combine high-plex and high-throughput spatial profiling, allowing researchers to rapidly and quantitatively assess the biological implications of heterogeneity within tissues. Since its launch, NanoString’s products have been amply described in prestigious scientific publications, and studies performed using NanoString’s products have been widely presented at industry conferences.

U.S. Patent No. 11,377,689 (the “’689 Patent”) represents a novel approach for the spatial detection and quantification of target analyte in a tissue sample. As its Abstract explains, the ’689 Patent is directed to an improved and novel way of

spatially detecting target analytes in regions of interest. Ex. 1001 (“’689 Patent”) at Abstract. More specifically, the method claimed in the ’689 Patent permits the simultaneous, multiplexed detection and quantification of protein and/or nucleic acid expression in a user-defined region of a tissue, cell, and/or subcellular structure within a cell, while maintaining the morphological context of the sample. The claimed invention of the ’689 Patent is an improvement over prior means of detecting target analytes in a sample. Conventional immunohistochemical methods allowed for simultaneous detection of six to ten protein targets at most. Similarly, in situ hybridization methods were limited to less than ten nucleic acid targets. *Id.* at 16:30-35. Thus, these methods do not enable the simultaneous detection of a large number of genes, proteins, or other biologically active molecules in the same sample. While laser microdissection methods are able to capture many genes, they are limited to a small number of locations and are cost prohibitive.

The claimed invention of the ’689 Patent uniquely addresses and solves these problems. The invention offers a spatial profiling method for RNA and/or protein in a tissue sample of much higher plex and sensitivity than previously available, providing researchers the ability to look at many biological targets at many locations in the same sample at the same time. As the ’689 Patent explains, the “present disclosure provides detection of large combinations of nucleic acid targets and/or

protein targets from a defined region of a sample. The present disclosure provides an increase in objective measurements by digital quantification and increased reliability and consistency, thereby enabling comparison of results among multiple centers.” *Id.* at 16:37-43. Specifically, more than 1000 targets can be detected, and there is “no pre-defined upper limit to the number of regions of interest and comparisons that can be made.” *Id.* at 16:21-23; 40:61-64. Furthermore, the invention is compatible with existing, readily available sequencing technologies, making it accessible to a large number of users. *Id.* at Abstract. The invention also allows for an economical assay design, as inexpensive and widely available synthetic DNA oligonucleotides can be used instead of more expensive probes. *Id.* at 37:50-55.

The claimed methods allow for the multiplexed detection and quantification of protein or nucleic acid expression in a way that preserves their spatial location across a tissue sample.

Accused by NanoString of infringing the ’689 Patent, 10X now asks the Board to institute review on all 30 claims of the ’689 Patent based on four grounds. These grounds, however, lack merit. We ask the Board not to institute review.

Grounds 1, 2, and 3 all rely on a reference by So et al. (“So-456”). *See* Ex. 1005. These grounds — whether based on anticipation or obviousness —

necessarily fail, as So-456 does not disclose at least four claim elements required by the '689 Patent claims. As documented herein, So-456 discloses nothing more than a speculative and unproven scheme that is nowhere close to the claimed inventions of the '689 Patent.

First, while all of the '689 Patent claims require collecting the nucleic acid probes that are bound to the target analyte in the tissue sample, So-456 is directed to the capture of amplification products that are *not* bound to the target analyte and that never were bound. Thus, So-456 teaches collection of entirely different molecules than required by the '689 Patent claims. Petitioner offers only conclusory statements that attempt to equate the probes with the amplification products.

Second, So-456 does not disclose treating a tissue sample to facilitate binding of nucleic acid probes to the target analyte, as required by all of the '689 Patent claims. Recognizing this dearth of disclosure, Petitioner points to other processes involving a tissue sample. Those processes, however, are unrelated to the binding of nucleic acid probes to the target analyte and do not disclose this element of the claimed invention.

Third, So-456 does not disclose a required extension reaction that incorporates a nucleic acid that identifies a location of the tissue sample, also required by all of the '689 Patent claims. While Petitioner concedes the absence of this claim

element, Petitioner insists that the claim element is either inherent or obvious. Neither contention is persuasive, however, as Petitioner fails to meet the burden to demonstrate inherency and provides only conclusory statements of motivation to combine relating to obviousness.

Fourth, So-456 does not disclose forming ligated probes from nucleic acid probes. While the '689 Patent describes this required element in detail, So-456 provides no disclosure on how two nucleic acid probes are ligated. As such, So-456 is ambiguous and cannot form the basis of anticipation or obviousness for this claim element.

Due to the missing claim elements, So-456 does not anticipate or render obvious the claims of the '689 Patent (Grounds 1 and 2). Petitioner's reliance on So-456 with Stahl to argue obviousness (Ground 3) also fails, as Petitioner does not rely on Stahl to provide the missing claim elements.

Finally, Petitioner makes a strained argument that the '689 Patent is not entitled to any priority due to inadequate written description. Petitioner's written description argument fails on the merits because the priority application adequately describes the invention claimed by the '689 Patent.

Petitioner fails to meet the burden of demonstrating a reasonable likelihood of prevailing with respect to at least one of the challenged claims. The Petition should be denied.

## **II. BACKGROUND**

### **A. The '689 Patent**

The '689 Patent is directed to a method of spatially detecting target analytes in regions of interest. This method can detect and quantify proteins and/or nucleic acids from particular locations in a tissue sample. Specifically, the '689 Patent relates to “probes, compositions, methods, and kits for simultaneous, multiplexed detection and quantification of protein and/or nucleic acid expression in a user-defined region of a tissue, user-defined cell, and/or user-defined subcellular structure within a cell that are adaptable for use with existing sequencing technologies.”

'689 Patent at Abstract. Claim 1 recites:

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 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.

'689 Patent Claim 1.

The claimed methods are directed to the spatial detection of target analyte in a first and second location of a tissue sample. At a high level, the method involves contacting a treated tissue sample with a plurality of nucleic acid probes that bind to a target analyte in the tissue sample, collecting the bound nucleic acid probes that bind to the target, performing an extension reaction on the collected nucleic acid

probes to incorporate a nucleic acid sequence that identifies a location, and identifying the location of the extension products via sequencing. Claims 2-15 depend on claim 1.

Claim 16 is also an independent claim:

16. 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 first plurality of nucleic acid probes and a second plurality of nucleic acid probes,

wherein each of the nucleic acid probes in the first plurality of nucleic acid probes comprise a target binding domain that binds to the at least one target analyte,

wherein each of the nucleic acid probes in the second plurality of nucleic acid probes comprise a target binding domain that binds to the at least one target analyte,

wherein the tissue sample is treated to facilitate binding of the first plurality of nucleic acid probes and the second plurality of nucleic acid probes to the at least one target analyte;

b) forming ligated probes by ligating each of nucleic acid probes from the first plurality of nucleic acid probes and each of nucleic acid probes from the second plurality of nucleic acid probes that are bound to each of identical molecules from the at least one target analyte;

c) collecting the ligated probes, or portions thereof, bound to each of the identical molecules from the at least one target analyte in a first location of the tissue sample under conditions that release the ligated probes, or portions thereof, from the first location of the tissue sample;

d) collecting the ligated probes, or portions thereof, bound to each of the identical molecules from the at least one target analyte in a second location of the tissue sample under conditions that release the probes, or portions thereof, from the second location of the tissue sample;

e) 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 ligated probes, or portions thereof, collected in step (c), thereby forming a first plurality of extension products that comprise the ligated probes, or portions thereof, collected in step (c) and the at least one nucleic acid sequence that identifies the first location of the tissue sample;

f) 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 ligated probes, or portions thereof, collected in step (d), thereby forming a second plurality extension products that comprise the ligated probes, or portions thereof, collected in step (d) and the at least one nucleic acid sequence that identifies the at least second location of the tissue sample; and

g) 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.

'689 Patent Claim 16. One difference between claims 1 and 16 is that the latter requires a first and second plurality of nucleic acid probes. The two plurality of nucleic acid probes are ligated to form ligated probes that are used in subsequent steps. Claims 17-30 depend on independent claim 16.

The '689 Patent was issued on July 5, 2022, from U.S. Patent Application No. 17/476,707 ("707 Application"), filed on September 16, 2021. The '707 Application is a continuation of U.S. Patent Application No. 16/272,487 ("487 Application"), filed February 11, 2019, which claims priority to U.S. Provision

Applications Nos. 62/629,180, filed February 18, 2018, and 62/771,212, filed November 26, 2018. The specification of the '707 Application and the '487 Application are identical.<sup>1</sup>

**B. The Level Of Ordinary Skill In The Art**

For the limited purpose of this Preliminary Response, NanoString does not challenge the definition of a POSA set forth in the Petition. NanoString reserves the right to challenge this definition should the Petition be instituted.

**C. The Prior Art Cited In The Petition**

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

**1. SO-456**

So-456 is a PCT application entitled “Spatial Mapping of Nucleic Acid Sequence Information” that published on February 2, 2017, as No. WO2017/019456. Ex. 1005 (“So-456”). So-456 purports to provide “methods and compositions for spatial detection and analysis of nucleic acids in a tissue sample.” *Id.* at Abstract.

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<sup>1</sup> During prosecution of the '707 Application, the examiner did not issue a rejection based on 35 U.S.C. § 103. As such, NanoString had no opportunity to submit secondary considerations of nonobviousness and reserves the right to do so in the event the Board institutes review based on a ground involving obviousness.

However, So-456 is a speculative patent application that describes an incomplete method.

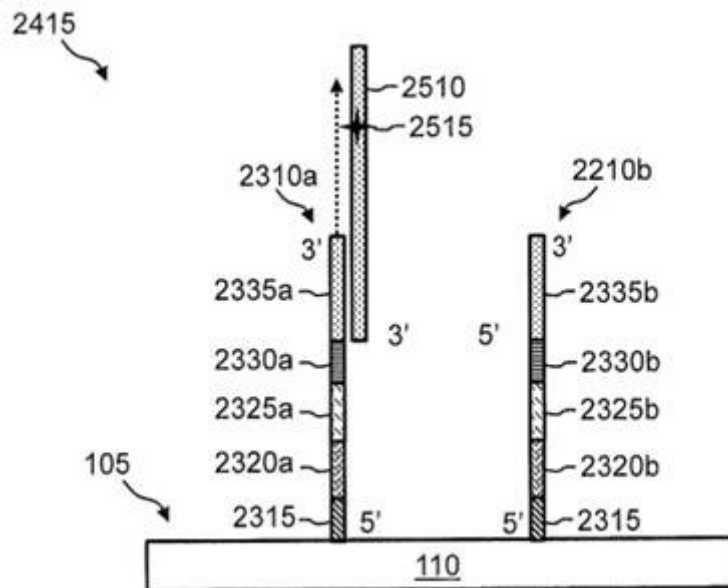
So-456 describes a method wherein first, “a tissue sample is prepared for analysis.” *Id.* ¶ [00152]. This includes using “fresh tissue,” “frozen tissue,” and “FFPE tissue sample that is sectioned onto a slide.” *Id.* Next, an optional step may take place wherein “an in situ reverse transcription reaction is used to synthesize cDNA from targeted mRNA in the tissue sample.” *Id.* ¶ [00153].

Subsequently, “a pair of gene-specific capture oligonucleotides that flank a region of interest are hybridized in situ to genomic DNA.” *Id.* ¶ [00178]. So-456, however, does not describe how the tissue sample must be treated to allow for this and subsequent steps to be performed in situ. Subsequently, “an in situ extension/ligation reaction is performed between the flanking capture oligonucleotides across the region of interest.” *Id.* at [00179]. So-456 does not describe what is “an in situ extension/ligation reaction.”

In the next step, So-456 describes amplifying the “DNA flanked by capture oligonucleotide ... to generate multiple copies of the region of interest, i.e., multiple genomic amplicons.” *Id.* at [00180]. The genomic amplicon are then “transferred onto an array and captured by hybridization to universal capture regions on the

array.” *Id.* at [00181]. In other words, So-456 teaches collecting the genomic amplicons, not the ligated probes.

After capture, So-456 describes performing an extension reaction to incorporate the target analyte sequence into the capture probe. The capture probe contains a spatial barcode sequence, a sequencing primer, and an optional cleavable region. *Id.* at Fig. 25A, ¶ [00302]. So-456 describes immobilizing the capture probes “such that the 3’-end is available for enzymatic extension.” *Id.* ¶ [00109]. This extension reaction is depicted in Figure 25A:



*Id.* at Fig. 25A. Thus, the extension reaction taught by So-456 incorporates the target analyte sequence onto a capture probe that already contains a SBS primer sequence and a spatial address region. The extension taught by So-456 does not incorporate any spatial barcode.

Following the extension reaction, a sequencing library is prepared, followed by sequencing. *Id.* ¶¶ [00156]-[00157]. The sequencing data is analyzed “to provide information as to the location of the nucleic acid in the tissue section.” *Id.* ¶ [00158].

Thus, unlike the '689 Patent claims, So-456 does not disclose a treated tissue sample, forming ligated probes, collecting ligated probes, or performing an extension reaction to incorporate a spatial barcode.

## 2. Stahl

Stahl is a *Science* article entitled “Visualization and analysis of gene expression in tissue sections by spatial transcriptomics” that published in 2016. Ex. 1016. The article purports to describe using “spatially barcoded arrays” that consists of unique barcodes and capture oligonucleotides on the surface of microscope glass slides. *Id.* at 8. By placing histological sections on the prepared arrays, “RNA-sequencing data with maintained two-dimensional positional information from [] mouse brain and human breast cancer” were collected to allow

“quantitative gene expression data and visualization of the distribution of mRNAs within tissue sections.” *Id.* at 1.

### 3. Chell

Chell is *not* prior art to the '689 Patent. Chell is a PCT application filed by 10X entitled “Methods for Spatial Analysis Using RNA-Templated Ligation” that published on July 1, 2021, as No. WO2021/133849. Ex. 1006. Chell purports to provide “methods of detecting an analyte of interest to interrogate spatial gene expression in a sample using RNA-templated ligation.” *Id.* at Abstract. Chell, however, was filed on December 22, 2020, *after* the priority date of the challenged '689 Patent.

### III. CLAIM CONSTRUCTION

Patent Owner does not dispute that the “collecting” steps in claims 1 and 16 includes the capture of entire probes. *See* Pet. at 15. Patent Owner, however, notes that a claim construction order has not been issued by the district court in the concurrent litigation.

**IV. THE PROPOSED GROUNDS DO NOT RENDER THE '689 PATENT INVALID**

**A. So-456 Does Not Anticipate or Render Obvious the Challenged Claims Because of Failure to Disclose Required Steps**

Petitioner relies on So-456 as the primary reference for Grounds 1, 2, and 3, arguing that So-456 anticipates or, in the alternative, renders obvious all of the claims of the '689 Patent. The Board should deny the Petition due to crucial technical differences between So-456 and the '689 Patent. So-456 provides a speculative design that was never put into practice and correspondingly limited details. The Board should deny the Petition due to crucial technical differences between So-456 and the '689 Patent. For example, Petitioner glosses over at least four required claim elements that So-456 does not disclose or render obvious. Specifically, So-456 fails to disclose (1) collecting the nucleic acid probes; (2) treated tissue sample; (3) an extension reaction to incorporate a nucleic acid sequence that identifies a location; and (4) forming ligated probes. These missing elements are required for independent claims 1 and 16, on which the remaining challenged claims depend. Accordingly, So-456 fails to anticipate or render obvious the challenged claims of the '689 Patent.<sup>2</sup>

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<sup>2</sup> The challenged dependent claims all depend on independent claims 1 and 16. For at least the given reasons, So-456 does not anticipate or render obvious

**1. So-456 Does Not Disclose Collecting the Nucleic Acid Probes**

First, So-456 does not disclose the “collecting” steps in independent claims 1 and 16. As required in claim 1, “nucleic acid probes, or portions thereof” that are “bound to the at least one target analyte” are collected:

*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;

’689 Patent Claim 1(b), 1(c).<sup>3</sup> Claim 16 similarly requires collecting “ligated probes, or portions thereof” that are “bound to each of the identical molecules from at least one target analyte”:

*c) collecting the ligated probes, or portions thereof, bound to each of the identical molecules from the at least one target analyte* in a first location of the tissue sample under conditions that release the ligated probes, or portions thereof, from the first location of the tissue sample;

*d) collecting the ligated probes, or portions thereof, bound to each of the identical molecules from the at least one target analyte* in a second

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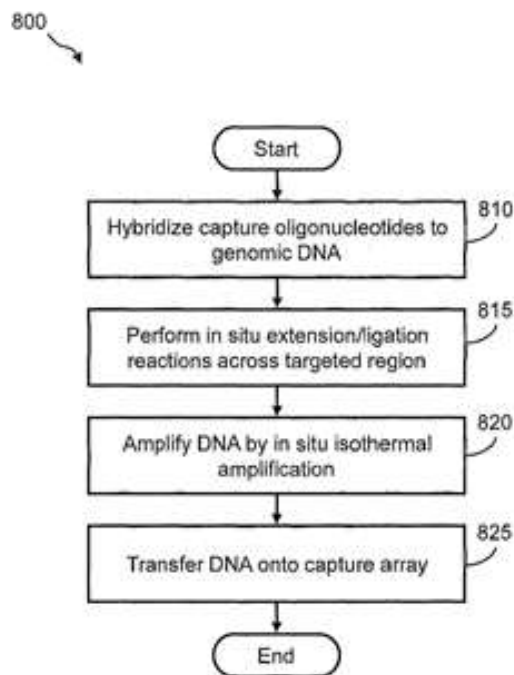
independent claims 1 and 16. Accordingly, So-456 also does not anticipate or render obvious dependent claims 2-15, 17-30. NanoString reserves the right to address the limitations in the challenged dependent claims should the Board institute review.

<sup>3</sup> Emphasis added throughout unless otherwise noted.

location of the tissue sample under conditions that release the [ligated] probes, or portions thereof, from the second location of the tissue sample;

'689 Patent Claim 16(c), 16(d). Thus, both independent claims require collecting probes or portions of probes that are bound to a target analyte.

So-456 does not disclose the “collecting” steps required in claims 1 and 16. Instead, as illustrated in So-456’s Figure 8, probes are amplified (step 820) and the *amplified products* are captured (step 825):



Ex. 1005 at Fig. 8. As So-456 describes, in Step 820, “DNA flanked by capture oligonucleotides is *amplified by in situ isothermal amplification* to generate multiple copies of the region of interest, i.e., multiple *genomic amplicons*.” *Id.* ¶

[00180]. Notably, So-456 asserts that the amplification step can occur *in situ*, but provides no detailed explanation or method to actually achieve this amplification. In the subsequent step, Step 825, “the **genomic amplicons** are transferred onto an array and captured by hybridization to universal capture regions on the array.” *Id.* ¶ [00181]. As such, while the “collecting” steps require capture of the probes, So-456 instead captures genomic amplicons, or **copies** of probes.

Petitioner fails to address this crucial distinction between the probes and the amplicons. If anything, Petitioner’s explanation of the method in So-456 further reinforces that **copies** of probes are captured—not the probes themselves:

After ligating the primary probe pairs, ***So-456’s method amplifies the ligated probes*** (950) “to generate multiple copies ... of the targeted region of interest” by “isothermal amplification,” ***generating unbound amplified ligated probes (“amplicons”).*** ***The amplified ligated probes*** (950) free from the target DNA molecules are “transferred from a sample . . . onto a capture array by passive diffusion” and “***captured*** onto the capture site 105” of the array.

Pet. at 20. Petitioner’s expert similarly states:

So-456’s method of Figures 8-9 specifies that the DNA molecules (950) formed in the previous step . . . are “***amplified by in situ isothermal amplification*** . . .” The amplicons generated by isothermal amplification are ***free from*** (i.e., ***not bound to***) ***the target nucleic acid molecules***. These amplicons (950) (i.e., ligated probes of the claim) are “***captured*** onto the capture site 105” of a spatially barcoded array, such as an array in Figure 1A.

Ex. 1002 ¶¶ 134-135. Thus, rather than capturing probes that are bound to a target analyte, So-456 discloses capturing amplicons that have never bound to a target analyte and are, as described by Petitioner, “unbound.” *See* Pet. at 20. Despite this notable difference between a bound probe and an amplicon, Petitioner argues that the capture of “amplified ligated probes (950)” discloses the required claim element.

Petitioner does not attempt to address the distinction between probes and amplicons. As the text of So-456 makes clear, item 950, which Petitioner refers to as “amplified ligated probes,” is referred to only as “DNA molecules” or “genomic amplicons.” *See* So-456 ¶¶ [00182]-[00183]. The term used by Petitioner, “amplified ligated probes,” is not present anywhere in So-456.

As the '689 Patent claims require capturing probes that are bound to a target analyte, products amplified from such probes are insufficient as they have not been bound to any target analyte. Accordingly, So-456 does not anticipate any of the '689 Patent claims because So-456 fails to disclose the required “capturing” step. *See Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1321 (Fed. Cir. 2003) (“Anticipation under 35 U.S.C. § 102 requires that a single prior art reference disclose each and every limitation of the claimed invention.”) (citation omitted).

## 2. So-456 Does Not Disclose Treated Tissue Sample

Independent from the above, So-456 also does not disclose the claim element regarding a treated tissue sample, as required in both independent claims 1 and 16.

As part of the “contacting” step, claim 1 requires a tissue sample that is “treated to facilitate binding of the nucleic acid probes to the target analyte”:

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 is treated to facilitate binding of the nucleic acid probes to the target analyte*;

’689 Patent at 145:54-59. Claim 16 also requires a “treated” tissue sample in its “contacting” step:

a) contacting the tissue sample with a first plurality of nucleic acid probes and a second plurality of nucleic acid probes, wherein each of the nucleic acid probes in the first plurality of nucleic acid probes comprise a target binding domain that binds to the at least one target analyte, wherein each of the nucleic acid probes in the second plurality of nucleic acid probes comprise a target binding domain that binds to the at least one target analyte, *wherein the tissue sample is treated to facilitate binding of the first plurality of nucleic acid probes and the second plurality of nucleic acid probes to the at least one target analyte*;

*Id.* at 147:57-148:4. Thus, the tissue sample must be “treated to facilitate binding” of nucleic acid probe to the target analyte.

So-456, however, provides no disclosure on treating a tissue sample to facilitate binding. The disclosure that is present in So-456 does not relate to facilitate binding of probes to target analyte in situ:

As used herein, the term “tissue sample” refers to a piece of tissue that has been obtained from a subject, fixed, sectioned, and mounted on a planar surface, e.g., a microscope slide. The tissue sample can be a formalin-fixed paraffin-embedded (FFPE) tissue sample or a fresh tissue sample or a frozen tissue sample, etc. The methods disclosed herein may be performed before or after staining the tissue sample. For example, following hematoxylin and eosin staining, a tissue sample may be spatially analyzed in accordance with the methods as provided herein. A method may include analyzing the histology of the sample (e.g., using hematoxylin and esoins staining) and then spatially analyzing the tissue.

Ex. 1005 ¶ [00125]. Sectioning, staining, and fixing a tissue sample on a microscope slide are not processes that “facilitate binding” of nucleic acid probes. So-456 instead describes introducing probes without any treatment to the tissue sample. *Id.* ¶ [0089] (“For example, nucleic acids from a tissue sample can be tagged by probes including location-specific sequence information (a ‘spatial address’).”). Without treatment, however, it is unclear how a nucleic acid probe can bind a target analyte in situ in a tissue sample that has been, for example, fixed by FFPE.

So-456’s lack of disclosure is jarring when compared to that in Chell. As Petitioner contends, “Chell teaches that the tissue sample is ‘deparaffinized,’

‘decrosslinked,’ and then ‘*treated with pre-hybridization buffer*’ before contacting the tissue with the probes.” Pet. at 60 (emphasis in original). As emphasized by Petitioner and its expert, these “processes allow [water-soluble] solutions (such as those containing the probes) to penetrate the tissue and bind the target analyte.” *Id.*; Ex. 1002 ¶ 301. As none of these processes are present in So-456, So-456 fails to disclose the claim element of treated tissue sample.

Petitioner attempts to argue around this lack of disclosure by taking language from So-456 out of context. Under Petitioner’s argument, the tissue sample is treated because “So-456 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. at 18 (citing Ex. 1005 ¶¶ [00152]–[00153]) (emphasis in original).

Paragraphs [00152] and [00153], however, do not describe treating a tissue sample to facilitate binding of nucleic acid probes:

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

[00153] At a step 215, ***in situ biochemistry is performed on the tissue section*** to facilitate subsequent manipulation of a nucleic acid in the sample. In some embodiments, ***an in situ reverse transcription reaction*** is used to synthesize cDNA from targeted mRNA in the tissue sample. In some embodiments, ***an in situ amplification reaction*** can

be used to produce multiple genomic DNA amplicons from targeted genes in the tissue sample. In some embodiments, there is no in situ biochemistry step, and synthesis of cDNA is performed after capture or extraction of the RNA from the tissue.

Ex. 1005 ¶¶ [00152]–[00153] (emphasis added). Paragraph [00152] describes sectioning a tissue sample onto a microscope slide and paragraph [00153] describes a reverse transcription reaction. Neither processes describe treating a tissue sample to facilitate binding of nucleic acid probes to a target analyte, unlike the “deparaffinized,” “decrosslinked,” and “treated with pre-hybridization buffer” processes cited by Petitioner for the Chell reference.

Accordingly, for this additional reason, So-456 does not anticipate or render obvious the challenged claims because So-456 fails to disclose a treated tissue sample. *See Moba, B.V.*, 325 F.3d 1306.

### **3. So-456 Does Not Teach Required Extension Reaction Steps**

Additionally, So-456 does not teach or render obvious the “extension reaction” steps required in independent claims 1 and 16. These claims require that “an extension reaction” be performed wherein a nucleic acid sequence that identifies the location of the target analyte is incorporated:

*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;

'689 Patent Claim 1(d); *see also id.* Claims 1(e), 16(e), 16(f).

So-456 does not disclose the required “extension reaction” step that incorporates a spatial barcode. Petitioner does not dispute this. Instead, Petitioner argues in Ground 1 that the required step is somehow inherent in So-456, or, alternatively in Ground 2, that So-456 renders the claimed extension reaction obvious. *See* Pet. at 23 (“Although So-456’s method ***does not explicitly describe*** the extension in Figures 8-9, So-456’s method inherently performs extension to achieve spatially barcoded nucleic acids for analysis.”); *see also* Ex. 1002 ¶ 139 (“Even though So-456’s method of Figures 8-9 ***does not expressly perform*** the claimed extension step, it does so inherently to achieve spatially barcoded nucleic acids for analysis.”); *id.* ¶ 217 (Even “assuming that So-456 does not teach the extension steps, claims 1 and 16 . . . would have been obvious over So-456.”).

**a. The Claimed Extension Step Is Not Inherent To So-456**

Petitioner must “meet a high standard” to establish that So-456 inherently discloses this limitation. *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014). Inherent anticipation requires that the limitation at issue “necessarily must be present, or the natural result of the combination of elements

explicitly disclosed by the prior art.” *Id.* at 1196. Inherency cannot be established “by probabilities or possibilities.” *Id.* (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). “The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *Id.* (citation omitted). Rather, a party must “show that *the natural result flowing* from the operation as taught would result in the performance of the questioned function.” *Id.* (emphasis in original).

Petitioner fails to meet this high standard. Petitioner does not—and cannot—demonstrate that the protocols disclosed in So-456 would *necessarily result* in incorporating the spatial address region via an extension reaction. Instead, Petitioner contends that because the ligated probes that are captured on the 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 to incorporate the “spatial barcode and sequencing primer-binding sites.” Pet. at 24.

To support its inherency argument, Petitioner primarily relies on Figure 9. Figure 9, however, does not disclose the claimed extension step for several crucial reasons. First, Figure 9 does not include a spatial barcode; thus, any extension reaction purported taught by Figure 9 certainly does not incorporate the claimed

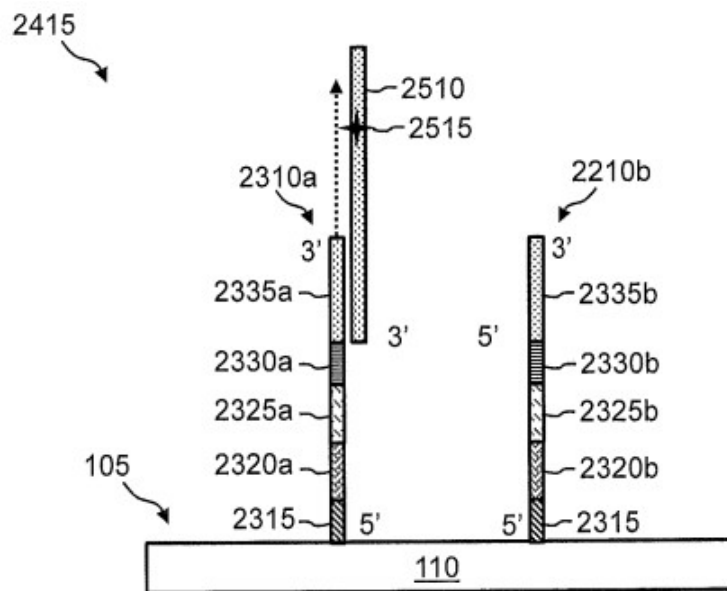
“sequence that identifies the . . . location of the tissue sample.” Petitioner contends that a region of the capture probe labeled “130” is the claimed spatial barcode. The description of Figure 9, however, is clear that region 130 is the sequencing by synthesis primer region.<sup>4</sup> Ex. 1005 ¶ [00182] (“SBS primer region 130 is SBS3”). For support that the 130 region is a spatial barcode, Petitioner looks to completely separate embodiments. Pet. at 24-25. Specifically, Petitioner cites paragraph [00141] describing Figure 1 as containing a “spatial address sequence.” *Id.* In fact, these figures come from entirely different sections of So-456. Figure 9 is included in the “Spatial Detection and Analysis of Nucleic Acid in a Tissue Sample” section while Figure 1 is found in the “Generation of Arrays” section. Ex. 1005 at 25, 29-38. Petitioner’s attempt to mix and match different embodiments fails because So-456 does not actually teach or disclose the claimed elements “arranged as in the claim.” *See NetMoneyIN, Inc., v. Verisign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008) (“Rather, our precedent informs that the ‘arranged as in the claim’ requirement applies to all claims and refers to the need for an anticipatory reference to show all of the limitations of the claims arranged or combined in the same way as

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<sup>4</sup> Petitioner agrees that item 130 in Figure 9 is a SBS primer region. *See* Pet. at 25 (citing So-456 ¶ [00182] for “SBS primer region 130 SBS3”) (modification omitted).

recited in the claims, not merely in a particular order. The test is thus more accurately understood to mean ‘arranged or combined in the same way as in the claim.’”).

Even if the capture probe of Figure 9 contains some spatial barcode, *in arguendo*, Petitioner’s argument still fails because So-456 includes numerous examples of uni-directional extension of the capture probe to incorporate the sequence of the target analyte. For example, a single extension reaction is clearly demonstrated by Figure 25A:

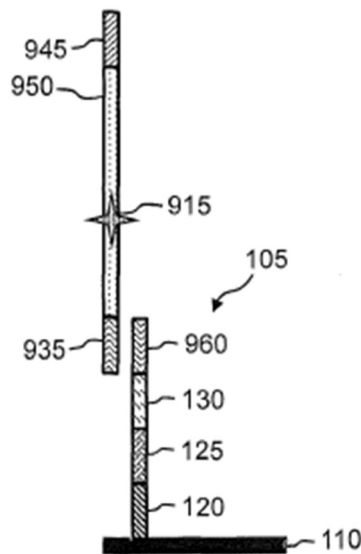


Ex. 1005 at Fig. 25A. As described by So-456, at this step, “first strand cDNA is synthesized using capture region 2335a as a primer in a reverse transcription reaction.” *Id.* ¶ [00316]. Numerous other examples provided by So-456 describe a similar uni-directional extension reaction using the capture region (labeled 2335a in the above figure) as a primer to copy the DNA sequence from the captured probe

(labeled 2510 in the above figure). *Id.* at Figs. 22, 23A, 24, 25A, 25B, 29A, 39, 40; *see also id.* ¶¶ [00297]-[00301], [00307]-[00320], [00332]-[00334], [00391]-[00395], [00410]-[00412] (“Capture probe [] hybridizes to nucleic acid molecule [] from a tissue sample and is extended to form a complementary nucleic acid molecule”). Importantly, none of the disclosed extension reactions incorporate a “sequence that identifies the first [and second] location of the tissue sample into each of the ligated probes.” Given these numerous examples of uni-directional extensions that do not incorporate the target analyte sequences onto capture probe, there is no reason that the step of incorporating a target analyte into a capture probe would be inherent to So-456. Even if the capture probe contains a “spatial address region,” as alleged by the Petitioner, that sequence is not incorporated by any of the methods taught by So-456.

Thus, in the embodiment relied on by Petitioner, represented by Figure 9, a single extension reaction takes place to incorporate the sequence of the target analyte into the capture probe on the capture site. This extension adds the target analyte sequence to the capture probe that Petitioner mistakenly alleges to contain the SBS primer region and spatial address region. *Id.* ¶¶ [00182]-[00183]. So-456 explicitly discloses such an extension because, as Petitioner notes, the capture probe is explicitly “available for enzymatic extension.” Pet. at 40; Ex. 1005 ¶ [00109].

Contrary to these disclosures, Petitioner contends that a “bi-directional” extension is necessarily occurring. Pet. at 25-26. Petitioner relies on a version of So-456’s Figure 9 annotated by Petitioner’s expert to demonstrate the “bi-directional” extension. *Id.* Neither Figure 9, nor the accompanying description, support Petitioner’s contention:



Ex. 1005 at Fig. 9. As is clear from the unannotated version of Figure 9, no “bi-directional” extension is *necessarily* occurring. Nowhere in the figure or description is a “bi-directional” extension reaction described. *Id.* at Fig. 9, ¶¶ [00182]-[00183]. Petitioner fails to point to any embodiment in So-456 wherein such a bi-directional extension takes place. In contrast, as discussed above, So-456 provides numerous embodiments wherein a uni-directional extension occurs.

Petitioner also contends, without evidence, that the extension reaction in Figure 9 is necessarily bi-directional because “So-456 did not teach methods for preventing the extension from occurring.” Pet. at 25. Such attorney argument is insufficient to show that bi-directional extension must necessarily occur. Moreover, in contrast to Petitioner’s argument, So-456 explicitly teaches methods for preventing extension. For example, So-456 provides that in “particular embodiments some or all of the nucleotide monomers can include reversible terminators.” Ex. 1005 ¶ [00601]. So-456 points to several other approaches of terminator chemistry that can be used to “block extension.” *Id.*

Accordingly, Petitioner fails to establish that the claimed “extension reaction that incorporates at least one nucleic acid sequence that identifies the first [and second] location of the tissue sample into each of the ligated probes” is necessarily present or is the natural result of the proposed method described in So-456.

**b. So-456 Does Not Render The Claimed Extension Step Obvious**

Petitioner’s Ground 2 argues in alternative to the Ground 1 inherency theory—that “the claimed extension steps would have been obvious to a POSA in view of So-456.” Pet. at 39. To support their obviousness argument, Petitioner relies on substantially the same argument that they rely on to argue inherency. *Id.* at 39-43. For example, Petitioner again argues that “the ligated probes captured on

the array” “include only one SBS primer binding site” and do not include a spatial barcode sequence. *Id.* at 40. Further, Petitioner repeats their argument that extension would necessarily be “bi-directional” because the capture probes are “unblocked.” *Id.*

For the same reasons discussed above, So-456 does not render obvious the required extension reaction steps because So-456 does not disclose an extension step (as admitted by Petitioner) that incorporates a spatial barcode and, further, Petitioner fails to establish that it would not have been obvious to modify the methods of So-456 to do so.

There is no disclosure in So-456 that any extension reaction is “bi-directional.” Petitioner simply states, without evidence, that such a reaction could occur and that So-456 “*suggests* the enzymatic extension of the 3’-ends of the capture probes and the ligated probe to incorporate a spatial barcode.” Pet. at 41. As discussed above, however, an extension of the 3’-end of the capture probes would not incorporate a spatial barcode because the capture probe does not contain any spatial address region. Ex. 1005 at Fig. 9, ¶¶ [00182]-[00183]. As Petitioner notes, the capture probe is explicitly “available for enzymatic extension.” Pet. at 40; Ex. 1005 ¶ [00109]. Thus, So-456 describes an enzymatic extension from the capture probe to incorporate the target analyte sequence. The extension from the

capture probe would not incorporate a spatial barcode because there is no spatial barcode at this location to incorporate. As such, So-456 does not disclose the claimed extension step.

Petitioner provides no compelling reason to modify the method of So-456 that would render it obvious. Petitioner contends that a POSA would have been motivated to modify SO-456's teaching because it was a "well-known, obvious, and routine technique for incorporating the spatial barcode (and necessary second sequencing primer)." Pet. at 42. Petitioner's purported motivation fails, however, because an extension of the captured probe is not necessary or obvious to achieve incorporation of the spatial barcode nor the sequencing primer. Petitioner contends that the capture probe already contains both the SBS primer and the spatial address region. *Id.* at 24-25. As discussed above, 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. Thus, this uni-directional extension of the *capture* probe would purportedly create a single molecule with both SBS primers, a spatial barcode (under Petitioner's theory), and the target analyte sequence. There would not be a motivation to modify the method to find an alternative where the purported motivation is already achieved with the disclosed method.

The use of inherency in the obviousness context must “be ‘carefully circumscribed’ because ‘that which may be inherent is not necessarily known and that which is unknown cannot be obvious.’” *Vivint, Inc. v. Alarm.com Inc.*, 741 Fed. Appx. 786, 792 (Fed. Cir. 2018) (quoting *Honeywell Int’l Inc. v. Mexichem Amanco Holding S.A.*, 865 F.3d 1348, 1354-55 (Fed. Cir. 2017)). Petitioner fails to meet this high burden.

Accordingly, So-456 does not anticipate or render obvious the claimed extension steps.

#### **4. So-456 Does Not Disclose Forming Ligated Probes**

Contravening independent claim 16, So-456 does not disclose ligating nucleic acid probes to form ligated probes. While claim 16 requires ligating two nucleic acid probes to form a ligated probe, So-456 discloses an unexplained “extension/ligation reaction” between two probes that are not adjacent.

As stated in claim 16(b), ligated probes must be formed by ligating nucleic acid probes:

**b) *forming ligated probes by ligating each of nucleic acid probes*** from the first plurality of nucleic acid probes and each of nucleic acid probes from the second plurality of nucleic acid probes that are bound to each of identical molecules from the at least one target analyte;

'689 Patent at 148:5-10 (emphasis added). Therefore, each ligated probe must be formed by ligating a nucleic acid probe from the first plurality of nucleic acid probes to a nucleic acid probe from the second plurality of nucleic acid probes.

Thus, two nucleic acid probes must be ligated to satisfy this claim. The '689 Patent teaches that the "first nucleic acid probe and the second nucleic acid probe can hybridize to the identifier oligonucleotide such that the first and the second nucleic acid probes are adjacent and are not overlapping." *Id.* at 25:51-54. The '689 Patent also teaches that a POSA can ligate "the first and the second nucleic acid probes, together, by performing a nick repair reaction." *Id.* at 25:64-65.

The '689 Patent repeatedly discloses that adjacent first and second nucleic acid probes are ligated together. *See, e.g., id.* at 6:33-38 ("wherein the first and the second nucleic acid probes hybridize to the identifier oligonucleotide such that the first and the second nucleic acid probes ***are adjacent but not overlapping***; (5) ***performing nick repair*** such that the hybridized first and second nucleic acid probes are ligated together;") (emphasis added), 5:66-6:3, 8:42-47, 9:13-18, 12:48-52, 27:42-47, 28:35-40, 30:53-58, 69:22-26, 70:63-67. A "nick repair" is specifically listed as a form of ligation. *See id.* at 13:9-11 ("In all methods of the present disclosure, the ligation process can be a nick ligation process. The nick ligation process can be a nick repair process.").

As Petitioner concedes, So-456 discloses two nucleic acid probes that are “not adjacent and are not overlapping.” *See* Pet. at 19; *see also* Ex. 1005 ¶ [00182] (“At step 810, a first gene-specific capture oligonucleotide 920 and a second gene-specific capture oligonucleotide 925 that *flank a region of interest* are hybridized in situ to DNA molecule 910.”). Thus, an “extension/ligation reaction” is performed across an unspecified number of nucleotides comprising the “region of interest.” *See, e.g., id.* ¶ [00179] (“At step 815, an extension/ligation reaction is performed in situ between the flanking capture oligonucleotides 920 and 925 *across the region of interest.*”). The extension/ligation reaction of So-456 requires an extension reaction prior to the ligation reactions because the probes are not adjacent. Thus, the ligation reaction taught by So-456 is *not* “ligating each of nucleic acid probes” together, but rather ligating the extension products together after the extension reaction occurs.

Petitioner argues that So-456 includes the “forming ligated probe” claim element due to the “extension/ligation reaction.” *See* Pet. at 19. Petitioner errs, however, in equating the “extension/ligation reaction” of So-456 with the method of “ligating each of nucleic acid probes” claimed by the ’689 patent. So-456 does not disclose actually ligating the probes. Instead, So-456 describes the process of ligating the *extension products*, not probes, in vague terms: “Perform in situ

extension/ligation reactions across targeted region.” Ex. 1005 at Fig. 8; *see also id.* ¶ [00179] (“At step 815, an extension/ligation reaction is performed in situ between the flanking capture oligonucleotides 920 and 925 across the region of interest.”). Thus, So-456 at most describes ligating the extension products together—not the probes.

As such, Petitioner’s argument that So-456’s “extension/ligation reaction” is equivalent to the “forming ligated probes” in claim 16(b)—which includes “a nick repair reaction”—is legal error. Petitioner’s reliance on their expert’s annotated figure is similarly misplaced. *See* Pet. at 19. Without explanation, Petitioner’s expert simply labels the unclear “extension/ligation reaction” as a “ligation.” Petitioner, however, cannot generate disclosure through their expert’s annotation.

Accordingly, Petitioner fails to show that So-456 discloses “forming ligated probes,” providing another independent ground to reject the Petition.

#### **B. Chell Does Not Anticipate Claims 1-30**

Ground 4 hinges on the notion that the claims fail the written description requirement because the specification fails to adequately disclose “collecting whole probes” and “a particular arrangement and usage of primary (analyte-binding) probes.” Pet. at 53, 55. Under the correct legal standard, however, the specification includes an adequate written description of the claimed methods and

their use. Specifically, the Petitioner’s purported ground of unpatentability is predicated on a determination that the challenged claims are not entitled to the September 16, 2021, priority date because its specification does not provide § 112 support for the challenged claims.<sup>5</sup>

The ’689 Patent is a direct continuation from the ’487 Application, both of which undisputedly share an identical disclosure.<sup>6</sup> As described below, the claimed invention of the ’689 Patent is adequately described by the ’487 application. Thus, the ’689 Patent is entitled to claim priority to at least the filing date of the ’487 Application—prior to the publication of Chell. Thus, Chell is not prior art.

**1. “Collecting Whole Probes” Is Adequately Described**

Petitioner contends that the claims fail the written description requirement because “collecting whole probes” is not adequately described. *Id.* The specification, however, discloses embodiments whereby the entire probe is cleaved and collected—exactly what is claimed.

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<sup>5</sup> The ’689 patent is entitled to claim priority to at least September 16, 2021, the filing date of application No. 16/272,487, because the ’689 patent is a continuation and thus shares identical disclosure. The ’689 patent is further entitled to claim priority to applications Nos. 62/771,212 and 62/629,180. Priority to these applications, however, is not necessary to exclude Chell as prior art. Thus, priority analysis for these applications is not necessary for this response. NanoString reserves the right to claim priority to applications Nos. 62/771,212 and 62/629,180.

<sup>6</sup> Although the ’689 Patent and the ’487 Application contain the same disclosure, for purposes of analytical purity, the discussion herein cites to the ’487 application.

First, despite Petitioner's repeated claims that the priority applications "never disclose releasing or collecting *whole* probes," Petitioner points to exclusively "non-limiting" embodiments to support their contention. Pet. at 53-54. For example, Petitioner points to '487 Application paragraph 246, which provides:

A probe of the present disclosure can include a region which permits the release of an identifier oligonucleotide following the application of a suitable force. ***In one non-limited example, the region is a cleavable motif (e.g., a restriction enzyme site or cleavable linker).*** The cleavable motif allows release of an identifier oligonucleotide from a bound target nucleic acid or protein and the identifier oligonucleotide can then be collected and detected. The region which permits the release of an identifier oligonucleotide can be positioned between the target-binding domain and the identifier oligonucleotide, allowing for the release of the identifier oligonucleotide from the target binding domain.

Ex. 1009 ¶ [246]; *see also id.* ¶¶ [00107], [00123]-[00127], [00131], [00140]-[00145], [00159], [00176], [00180], [00184], [00200]-[00201], [00211], [00221], [00236], [00315]-[00317]. Petitioner points to non-limiting embodiments because the patents do in fact disclose embodiments where the whole probe is released and collected.

For example, the patent provides certain embodiments wherein the entire "intact probe" is collected. *Id.* ¶ [252]. Specifically, this is an embodiment where the entire probe is collected. The '487 Application describes an optional purification step wherein background noise "during nucleic acid detection, can be

reduced by performing a negative purification of the *intact probe molecule*.” *Id.* To be clear, contrary to Petitioner’s argument, this embodiment describes *both* the identifier oligonucleotide and the target binding domain being collected together. *Id.* To ease the optional purification step, which removes the target binding domain after collection, “a universal purification sequence may be included in a probe, e.g., in the target binding domain.” *Id.* Thus, the target binding domain, along with the identifier oligonucleotide, can be collected. To say otherwise renders the “purification sequence” useless.

Further, the patent is clear that these collected “intact probes” can be used to detect target analytes. The ’487 Application provides that as “described in the preceding, probes of the present disclosure can be used to detect a target nucleic acid or target protein present in any sample, e.g., a biological sample.” *Id.* ¶ 261. Thus, contrary to Petitioner’s contentions, the ’487 Application describes the cleaving steps as one optional embodiment, but it is not intended to limit the scope.

Therefore, “collecting whole probes” is adequately described in the ’689 Patent.

## 2. “On-Analyte Ligation” Is Adequately Described

Petitioner contends that the claims fail the written description requirement because “on-analyte ligation” is not adequately described. Pet. at 55-57. Again, Petitioner is wrong on the merits.

First, Petitioner attempts to create a distinction between “primary” and “secondary” probes. *Id.* at 55-56. The ’487 Application, however, never uses either “primary” or “secondary” or any synonym to describe the probes. *See generally* Ex. 1009. Petitioner creates this artificial distinction to discuss what it refers to as the “off-analyte” and “on-analyte” steps. Pet. at 55-56. Again, these terms do not appear anywhere in the ’487 Application. *See generally* Ex. 1009.

Petitioner points to non-limiting embodiments in the ’487 Application to support their contention that the particular arrangement claimed by the ’689 Patent is not adequately described. The embodiments in the ’487 Application are not limiting, however, and a skilled artisan at the time would have understood the ’487 Application to be in possession of a method wherein the hybridization and ligation steps occur while the identifier oligonucleotide is “on-analyte.” The particular sequence of steps in the non-limiting embodiments Petitioner points to do not affect the claim of priority.

Nowhere does the '689 Patent or the '487 Application describe the ligation step as inventive or unique. In fact, ligation was a well-known technique at the time of the invention. The ligation reaction is merely a standard technique for attaching the adjacent nucleic acid sequences—the first nucleic acid probe and the second nucleic acid probe. The ligation step is *not* the invention of the '689 Patent nor the '487 Application. Further, the timing of the ligation, or when the ligation occurs, is not crucial to the invention of the '689 Patent. References included with the '487 Application contain descriptions of ligation reactions, including ligations occurring while “on-analyte.” Ex. 1012 at 1543. For example, a 2004 article by Mats Gullberg entitled “Cytokine detection by antibody-based proximity ligation” (“Gullberg”), describes methods of “proximity ligation.” *Id.*; Ex. 2001 at Abstract. The proximity ligation taught by Gullberg involves “binding pairs of specific protein-binding reagents to the same target-protein molecule” in order to bring “oligonucleotides attached to the binding reagents in proximity” to each other. Ex. 2001 at 1. Then, “a mixture is added that contains all components required for ligation” and the two adjacent oligonucleotides are ligated together. *Id.* Thus, not only were methods of ligation well-known, but also methods for “on-analyte ligation.” The timing of the claimed ligation step does not change how the claimed

invention works or help to achieve the desired results. Thus, Petitioner's attempt to point to the timing of the ligation as crucial for priority is inapposite.

Moreover, the '487 Application provides methods for targeted application of reagents. For example, the '487 Application provides that "protein-targeting probes and nucleic acid-targeting probes may be applied." Ex. 1009 ¶ [00253]. A POSA would have been aware that, similarly, targeted application of reagents for ligation could have been applied. This disclosure is similar to the approach of Gullberg, where components required by ligation can be applied prior to the release of the probes. Thus, a POSA would have understood that the '487 Application adequately describes methods by which the ligation reaction could be performed prior to the release of probes—consistent with the claimed invention of the '689 patent. *See, e.g., Pandrol USA, LP v. Airboss Ry. Prods., Inc.*, 424 F.3d 1161, 1165 (Fed. Cir. 2005) ("The possession test requires assessment from the viewpoint of one of skill in the art."); *Scriptpro, LLC v. Innovation Assocs., Inc.*, 762 F.3d 1355, 1359 (Fed. Cir. 2014) (The "specification's description of embodiments having sensors for providing information about slot allocations and availability does not necessarily mean that the only described invention is a collating unit with such sensors.").

**V. CONCLUSION**

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

Dated: November 24, 2023

Respectfully submitted,

/Derek C. Walter/

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## **CERTIFICATE OF COMPLIANCE**

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 9,125 words as calculated by the “Word Count” feature of Microsoft Word 2016, the word processing program used to create it.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: November 24, 2023

By: /Derek C. Walter/  
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## **CERTIFICATE OF SERVICE**

I hereby certify that a true and correct copy of **PATENT OWNER'S PRELIMINARY RESPONSE TO PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 11,377,689 and EXHIBIT 2001** was served on November 24, 2023, via email pursuant to 37 C.F.R. and § 42.107 to the Petitioner at the addresses below:

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