

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC,
Petitioner,

v.

BRUKER SPATIAL BIOLOGY, INC.,
Patent Owner.

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

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

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EXHIBIT LIST

Exhibit No.	Description
EX2001	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).
EX2002	<i>In re: Nanostring Technologies, Inc., et al.</i> , No. 24-10160 (D. Del.), D.I. 235, Debtors’ motion for an order confirming, restating and enforcing the protections of Section 362 of the bankruptcy code with respect to inter partes review proceedings before the Patent Trial and Appeal Board
EX2003	<i>In re: Nanostring Technologies, Inc., et al.</i> , No. 24-10160 (D. Del.), D.I. 316, Order confirming, restating and enforcing the protections of Section 362 of the bankruptcy code with respect to inter partes review proceedings
EX2004	Declaration of Edward R. Reines
EX2005	In re Reines, No. 14-4, Dkt. No. 16 (Fed. Cir. Nov. 5, 2014)
EX2006	Expert Declaration of Dr. David H. Sherman, Ph.D.
EX2007	Transcript from Deposition of Paul Spellman on August 5, 2024
EX2008	U.S. Patent Application Publication No. US 2016/0194701 A1 (“Application No. 14/946,386” or “386 Application”)
EX2009	U.S. Patent Application Publication No. US 2010/0015607 A1 (“607 Publication”)
EX2010	U.S. Patent Application Publication No. US 2011/0086774 A1 (“774 Publication”)

EX2011	File History of U.S. Patent No. 11,377,689
EX2012	U.S. Patent Application Publication No. US 2011/0245111 A1 (“’111 Publication”)
EX2013	Sandeep Verma and Fritz Eckstein, “Modified Oligonucleotides: Synthesis and Strategy for Users,” <i>Annu. Rev. Biochem.</i> , Vol. 67, pp. 99-134, 1998
EX2014	Curriculum Vitae of Dr. David H. Sherman, Ph.D.
EX2015	IPR2022-00746, EX1072, Brown, T.A., Ed., “Chapter 4: Studying DNA,” <i>Genomes</i> , pp. 96-124, Second Edition, John Wiley & Sons, Inc., United States (2002)
EX2016- EX2049	Intentionally left blank
EX2050	<i>10X Genomics, Inc. and Prognosys Biosciences, Inc. v. Nanostring Technologies, Inc.</i> , No. 21-cv-653, D.I. 244 Petitioner’s Consolidated Brief (D. Del. Aug. 18, 2023), Exhibit 2050 from the deposition of Paul Spellman, taken on August 5, 2024
EX2051	U.S. Patent No. 11,008,607, Exhibit 2051 from the deposition of Paul Spellman, taken on August 5, 2024
EX2052	U.S. Patent Application Publication No. US 2016/0194701 A1, Exhibit 2052 from the deposition of Paul Spellman, taken on August 5, 2024

I. INTRODUCTION

U.S. Patent No. 11,377,689 (the “’689 Patent”) is directed to an improved and novel way of spatially detecting target analytes in regions of interest. EX1001 Abstract. Specifically, the claimed methods permit the simultaneous, multiplexed detection and quantification of protein and/or nucleic acid expression in a user-defined region of a tissue, cell, and/or subcellular structure within a cell, while maintaining the morphological context of the sample. The claimed invention of the ’689 Patent is an improvement over prior means of detecting target analytes in a sample, such as conventional immunohistochemical and in situ hybridization methods, which were limited to less than ten targets at most. *Id.* at 16:30-35. Other methods, such as laser microdissection, are limited to a small number of locations and are cost prohibitive.

Accused of infringing the ’689 Patent, Petitioner now asks the Board to invalidate all 30 claims of the ’689 Patent based on four grounds. These grounds, however, lack merit.

Grounds 1, 2, and 3 all rely on a reference by So et al. (“So-456”). EX1005. As documented herein, So-456 does not disclose at least four claim elements required by the ’689 Patent claims. Thus, Petitioner’s grounds, whether based on anticipation and/or obviousness, necessarily fail.

First, rather than collecting probes bound to the target analyte, So-456 is directed to the capture of amplification products that are never bound to the target analyte. Thus, the molecules that So-456 collects are entirely different from those required by the claims.

Second, So-456 fails to disclose treating a tissue sample to facilitate the binding of probes to the target analyte, as required by the claims. Petitioner fails to point to processes that accomplishes the claimed feature and also fails to show how a POSA would accomplish this.

Third, So-456 does not disclose a required extension reaction that incorporates a nucleic acid that identifies a location of the tissue sample. Petitioner's argument that this missing feature is either inherent or obvious likewise fails because a POSA would neither perform nor be motivated to perform this feature when using the So-456 method.

Fourth, So-456 does not disclose forming ligated probes from pairs of nucleic acid probes. So-456 does not disclose how probes are ligated and, in any event, fails to disclose the ligation required by the claims.

Due to the missing claim elements, So-456 does not anticipate or render obvious the claims of the '689 Patent. The inclusion of Stahl does not change this outcome, as Petitioner does not rely on Stahl to provide the missing claim elements.

Ground 4 relies on anticipation by Chell. Chell, however, is not prior art, despite Petitioner's arguments that the '689 Patent claims lack written description support for two features from the priority document, the '487 application. A POSA would understand both of these features to be disclosed.

Petitioner fails to meet the burden of demonstrating by a preponderance of the evidence that any of the '689 Patent claim are invalid. The Board should find in Patent Owner's favor.

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."

EX1001 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.

Id. Claim 1.

The claimed methods are directed to the spatial detection of target analyte in a first and second location of a tissue sample. At a high level, the method involves 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.

Id. 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.

B. The Level Of Ordinary Skill In The Art

A person having ordinary skill in the art ("POSA") relevant to the '689 patent as of February 11, 2019, would have had a Ph.D. in molecular biology, genetics, chemistry, biochemistry, organic chemistry, microbiology, or a related discipline, with at least two years of experience in the spatial detection of proteins and nucleic acids. EX2006 ¶¶ 21-23. Alternatively, a POSA would have been someone with greater relevant experience sufficient to compensate for having less relevant formal education. *Id.*

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

- Amplification and sequencing of nucleic acids, including PCR and next-generation sequencing.
- Design of oligonucleotide strands with specific sequences, including attachment of different labels or molecules.
- Ligating nucleic acids, including using ligases.
- Immunohistochemical and in situ hybridization methods.

EX2006 ¶ 24.

C. Petitioner's References

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. EX1005 (“So-456”). So-456 purports to provide “methods and compositions for spatial detection and analysis of nucleic acids in a tissue sample.” *Id.* at Abstract. 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.* ¶ 152. This includes using “fresh tissue,” “frozen tissue,” and

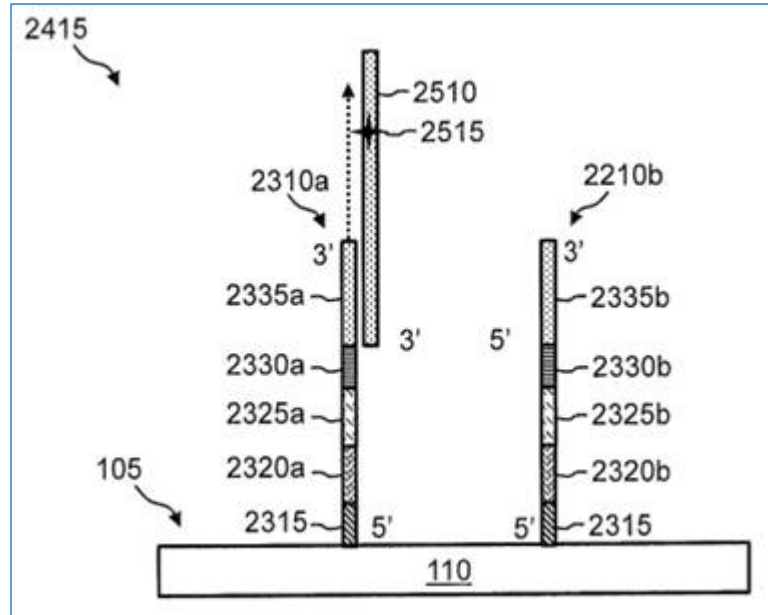
“FFPE tissue sample that is sectioned onto a slide.” *Id.* Next, an optional step may take place wherein “an in situ reverse transcription reaction is used to synthesize cDNA from targeted mRNA in the tissue sample.” *Id.* ¶ 153.

Subsequently, “a pair of gene-specific capture oligonucleotides that flank a region of interest are hybridized in situ to genomic DNA.” *Id.* ¶ 178. 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.* ¶ 179. 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.* ¶ 180. The genomic amplicons are then “transferred onto an array and captured by hybridization to universal capture regions on the array.” *Id.* ¶ 181. 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.* Fig. 25A, ¶ 302. So-456 describes immobilizing the capture probes “such that the 3’-end is available for enzymatic extension.” *Id.* ¶ 109. 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.* ¶¶ 156-157. The sequencing data is analyzed “to provide information as to the location of the nucleic acid in the tissue section.” *Id.* ¶ 158.

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. EX1016. 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 the 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 Genomics entitled “Methods for Spatial Analysis Using RNA-Templated Ligation” that published on July 1, 2021, as No. WO2021/133849. EX1006. Chell purports to provide “methods of detecting an analyte of interest to interrogate spatial gene expression in a sample using RNA-templated ligation.” *Id.* Abstract.

Chell, however, was filed on December 22, 2020, *after* the priority date of the challenged '689 Patent.

III. CLAIM CONSTRUCTION

Patent Owner notes that the district court in a concurrent litigation has issued a claim construction order, construing claim terms of the '689 Patent to have their plain and ordinary meaning. EX1052. The Board, in the Decision Granting Institution, construed the following terms:

- “Nucleic acid probe” – 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.
- “Collecting the nucleic acid probes” – 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.

Paper 14 at 23-24. To the extent the construction of “nucleic acid probe” refers to the use of an extension reaction to encode spatial information, Patent Owner applies the Board’s construction. Patent Owner also applies the Board’s construction of “collecting the nucleic acid probes.” EX2006 ¶¶ 25-28.

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

A. GROUND 1: SO-456 DOES NOT ANTICIPATE CLAIMS 1-8, 11-23, AND 26-30

Petitioner argues that So-456, either expressly or inherently, anticipates claims 1-8, 11-23, and 26-30 of the '689 Patent, including independent claims 1 and 16. For a prior art reference to anticipate a claim, it must meet a high bar, as anticipation “requires the presence in a single prior art disclosure all elements of a claimed invention arranged as in the claim.” *Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd.*, 807 F.3d1283, 1293 (Fed. Cir. 2015) (internal citations omitted). So-456 provides little more than a speculative design, with limited details. As detailed herein and in Dr. Sherman’s supporting declaration, Petitioner either glosses over key technical differences between the '689 Patent and So-456, or attempts to string together different embodiments from So-456 in contravention of Federal Circuit law. 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 elements are required for independent claims 1 and 16. Because So-456 fails to disclose these elements, it does not anticipate the independent claims of the '689

Patent, and accordingly does not anticipate any challenged claim of the '689 Patent.

EX2006 ¶¶ 35-36.

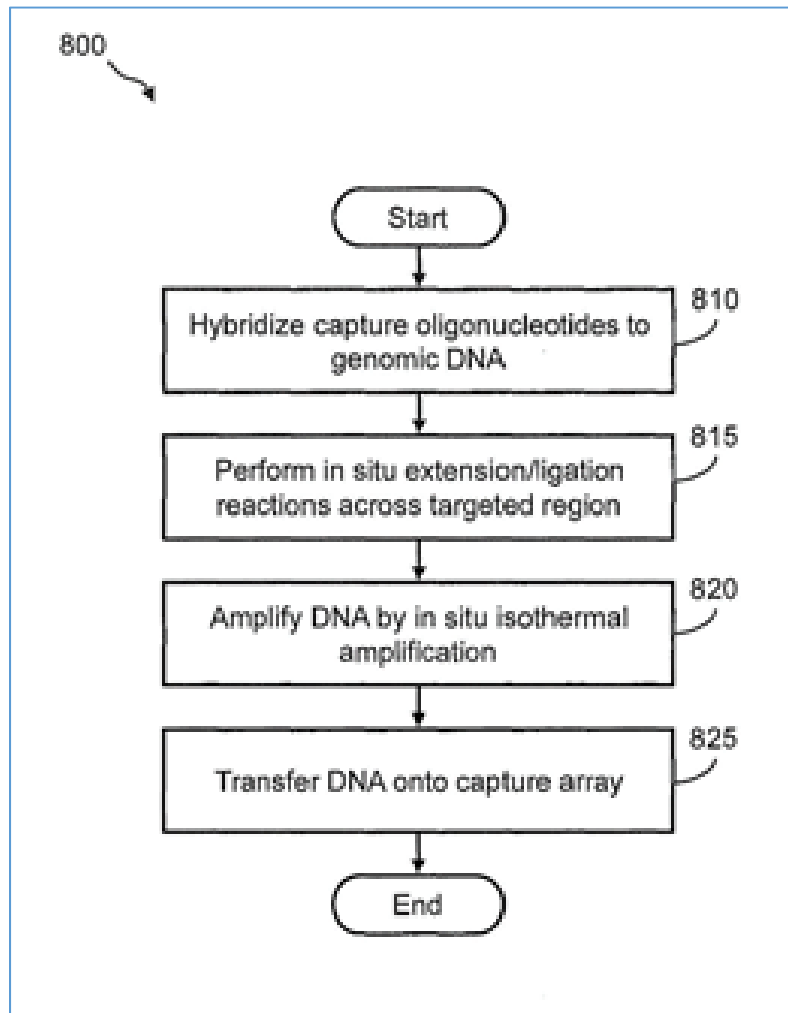
1. So-456 Does Not Disclose Collecting the Nucleic Acid Probes

So-456 does not disclose the “collecting” steps of independent claims 1 and 16. EX2006 ¶¶ 37-43. The independent claims of the '689 Patent require that “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;

EX1001 Claim 1(b); *see also id.* Claim 1(c), 16(c), 16(d) (Claim 16 reciting collecting “ligated probes, or portions thereof” that are “bound to each of the identical molecules from at least one target analyte.”).

So-456 does not disclose collecting nucleic acid *probes*, it discloses the collection of amplified products. Figure 8 demonstrates So-456's method:



EX1005 Fig. 8. As this depiction of So-456’s workflow makes clear, between hybridization and capture there are two steps—an “extension/ligation” reaction and an isothermal amplification step. EX1005 ¶ 180; EX2006 ¶¶ 39-40. All these reactions occur *in situ*, before any nucleotides are collected. *Id.* Indeed, collection does not occur until step 825, at which point ***amplicons*** are collected, not ***bound probes***. *Id.*

Petitioner does not address the distinction between amplicons and bound probes, and confirms that amplicons are collected. Petitioner explains that “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.’” Paper 2 at 20. Therefore, Petitioner (and Dr. Spellman) acknowledge that it is amplicons that are collected, including amplicons that have never been bound to a target. EX2006 ¶¶ 41-43. The Board also acknowledged the deficiencies in Petitioner’s argument in its Decision Granting Institution, stating that “Petitioner has not demonstrated that So-456 teaches this claim limitation [collecting the nucleic probes] or otherwise demonstrates that this limitations would have been inherent in the disclosure of So-456 for claims 1 and 16.” Paper 14 at 24.

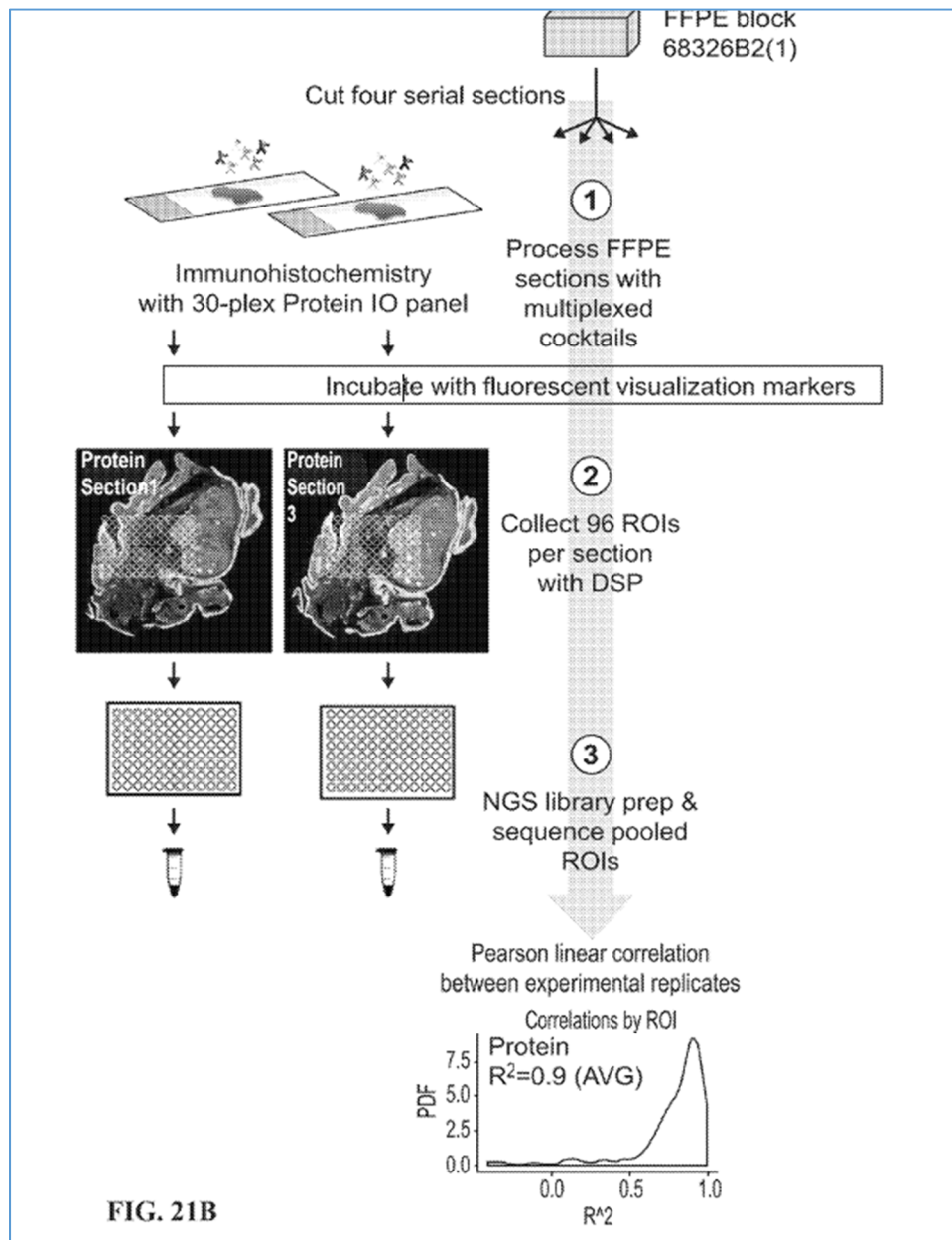
2. So-456 Does Not Disclose Treated Tissue Sample

So-456 does not disclose treating a tissue sample “to facilitate binding of the nucleic acid probes to the target analyte.” EX2006 ¶¶ 44-53. The first step of both Claim 1 and Claim 16, the “contacting” step, includes a limitation that requires treating the tissue sample:

- 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 to the target
analyte;*

EX1001 Claim 1(a); *see also id.* Claim 16(a) (reciting the same limitation). As Dr. Sherman explains, a skilled artisan would have recognized the importance of treating the tissue sample to facilitate the binding of the probes from the '689 Patent's disclosures. EX2006 ¶¶ 45-47. Figure 21B, for example, depicts a treatment step as part of an exemplary workflow:



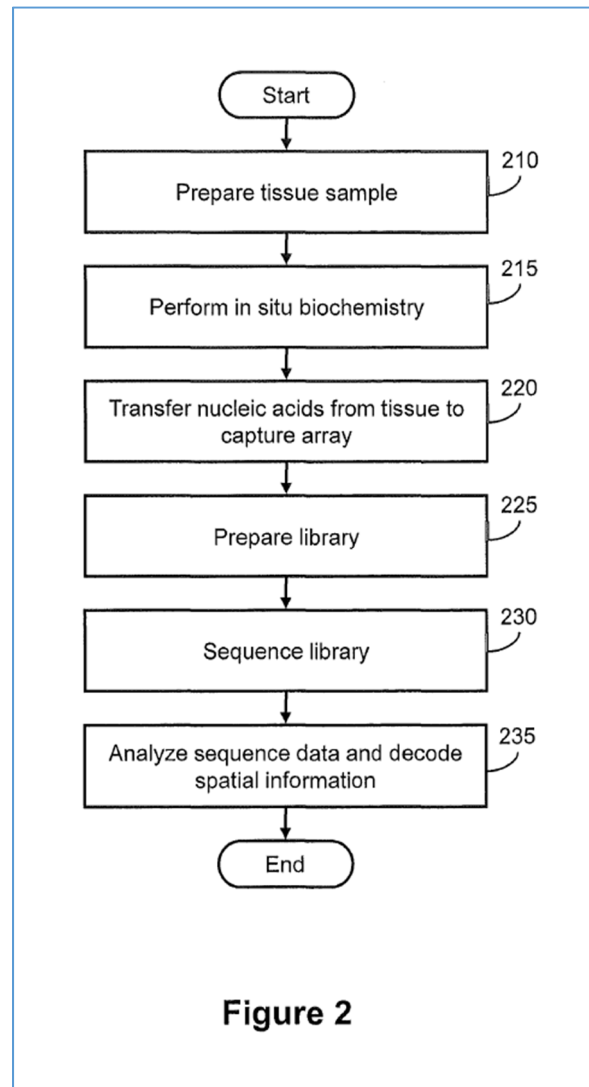
EX1001 Fig. 21B. The exemplary workflow begins with the use of an FFPE block. The first step is to cut serial sections directly from the block. Sectioning is followed by “process[ing]” the sections with “multiplexed cocktails” prior to incubation and further analysis. Such a step is an example of treating the tissue to

facilitate probe binding. EX2006 ¶ 45. Figure 22B, which depicts yet another exemplary workflow, also features a treatment step. *Id.*; EX1001 Fig. 22B. Further emphasizing the importance of a treatment step, Examples 7-9 all use an FFPE tissue sample (as used in the workflows depicted in Figures 21B and 22B). As Dr. Sherman explains, it would be impossible to analyze such tissue by contacting with probes without treating the sample to facilitate the binding of probes. EX2006 ¶¶ 46-47. Treatment of the tissue sample is also emphasized as important based on disclosures of, for example, using probes at concentrations lower than prior art techniques (such as immunohistochemistry and in situ hybridization). EX1001 at 40:4-8; EX2006 ¶ 47. That the treatment step is necessary to perform the analyses contained in the workflows of the '689 Patent is confirmed by the prosecution history of both the '689 Patent and its parent, the '487 Application. EX2006 ¶ 48. During the prosecution of the '487 Application, an identical treatment limitation was added to the claims as the limitation found in the '689 Application. EX1012.1560; EX2006 ¶ 49. Applicant cited to portions of the specification explaining that there are reagents, for example “buffers and other reagents, that are known in the art to be useful in facilitating binding of a protein or a nucleic acid in a sample,” and so it would be “well within the purview of a person of ordinary skill in the art” to treat a tissue sample as recited by the claim.

EX1012.1560. When the tissue treatment limitation was added to the claims that would be issued for the '689 Patent, Patent Owner highlighted to the Examiner that Examples 7-10 and Figures 21 and 22 enable a skilled artisan to practice the claimed invention. EX2011.270; EX2006 ¶¶ 48-49.

These disclosures from the '689 Patent are a sharp contrast from disclosures in So-456 that Petitioner relies upon. Petitioner relies on paragraphs 152 and 153 to argue 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 sample.” EX1005 ¶¶ 152-153. In context, however, these disclosures do not describe treating a tissue sample to facilitate probe binding. EX2006 ¶¶ 50-51. Paragraph 152 describes the preparation step as only sectioning a sample onto a slide. EX1005 ¶ 152; EX2006 ¶¶ 50-51. Paragraph 153 describes “in situ biochemistry,” but specifically describes a reverse transcription reaction to synthesize cDNA or an in situ amplification reaction to produce amplicons. EX1005 ¶ 153; EX2006 ¶¶ 50-51. In other words, the biochemistry does not facilitate probe binding—the disclosed biochemical reactions generate the amplicons that are ultimately bound. EX2006 ¶¶ 50-51.

Figure 2 depicts the workflow with the above-mentioned steps, and emphasizes the lack of a treatment step:



EX1005 Fig. 2. As shown above, the alleged treatment steps (210 and 215) occur before the step of transferring “nucleic acids from tissue to capture array,” but as is explained above and confirmed by Dr. Sherman, nothing in those steps *facilitates the binding of probes*. EX2006 ¶ 52. Because So-456 lacks disclosure of a treatment step and contains no disclosure that would lead a skilled artisan to

recognize the importance of treating a tissue sample to facilitate probe binding, So-456 does not anticipate the challenged independent claims. EX2006 ¶ 53.

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

Petitioner argues that 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.” Paper 2 at 23. Petitioner’s inherency theory fails. 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).

Claim 1 and Claim 16 require that an “extension reaction” is 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;

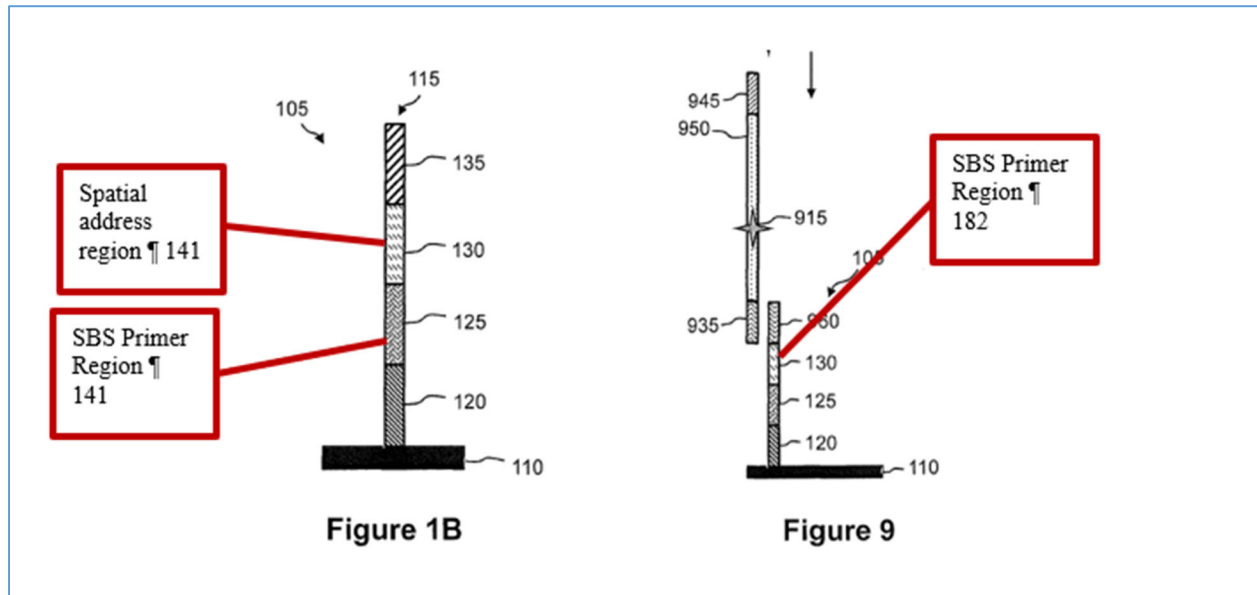
EX1001 Claim 1(d); *see also id.* Claims 1(e), 16(e), 16(f). Petitioner does not—and cannot—demonstrate that the protocols disclosed in So-456 would necessarily result in incorporating the spatial address region via an extension reaction. EX2006 ¶¶ 54-65. Instead, Petitioner contends that because the 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.” Paper 2 at 24.

First, as detailed above, So-456 does not disclose collecting bound probes. So-456 therefore cannot disclose any claim limitations requiring an extension

reaction performed on “each of the nucleic acid probes, or portions thereof, collected in” the relevant “collecting step,” e.g. claim 1(b), 1(c), 16(c), or 16(d). EX2006 ¶ 58.

Second, the disclosures that Petitioner relies upon do not inherently disclose an extension reaction as recited in claims 1 and 16. Petitioner relies primarily upon Figure 9, arguing that because “So-456’s ligated probes (950) captured on the array in the previous step are not yet tagged with a spatial barcode and do not include functional sequences...necessary for performing by sequencing-by-synthesis (SBS) in subsequent steps,” it is necessary that the extension step of Figure 9 must include an extension reaction as recited. Paper 2 at 24. Figure 9, however, does not include a spatial barcode. Any extension reaction purportedly 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. EX1005 ¶ 182 (“SBS primer region 130 is SBS3”); EX2006 ¶ 59. For support that the 130 region is a spatial barcode, Petitioner looks to completely separate embodiments. Paper 2 at 24-25. Specifically, Petitioner cites paragraph 141 describing Figure 1 as containing a “spatial address sequence.” *Id.* In fact, these figures come from

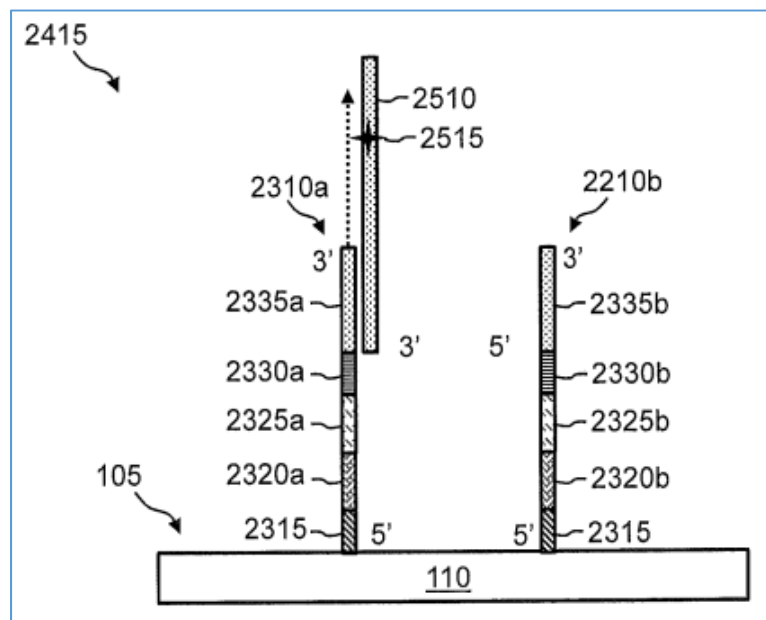
entirely different sections of So-456. EX2006 ¶ 60. Dr. Sherman's annotations to Figures 1B and Figure 9 clarify this difference:



EX2006 ¶ 60; EX1005 at Figures 1B, 9. As Dr. Sherman explains, a skilled artisan would not have recognized the spatial address region labeled in Figure 1B to be the same as the SBS primer region in Figure 9. EX2006 ¶ 60. 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 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 Figure 9 contained some form of spatial barcode (it does not), Dr. Spellman’s annotations as to bidirectional extension are misleading. So-456 includes numerous examples of uni-directional extension of the capture probe to incorporate the sequence of the target analyte. EX2006 ¶ 61. For example, a single extension reaction is clearly demonstrated by Figure 25A:



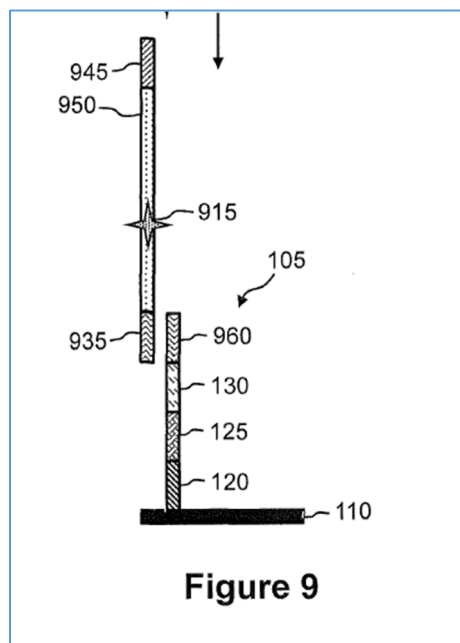
EX1005 Fig. 25A. As described by So-456, at this step, “first strand cDNA is synthesized using capture region 2335a as a primer in a reverse transcription reaction.” *Id.* ¶ 316. Numerous other examples provided by So-456 describe a similar uni-directional extension reaction using the capture region (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.* Figs. 22, 23A, 24, 25A, 25B, 29A, 39, 40; *see also id.* ¶¶ 297-301, 307-320, 332-334, 391-395, 410-412 (“Capture probe [] hybridizes to nucleic acid molecule [] from a tissue sample and is extended to form a complementary nucleic acid molecule”); EX2006 ¶ 61. 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.” EX2006 ¶ 62. Given these numerous examples of uni-directional extensions that do not incorporate the target analyte sequences onto a 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.* ¶¶ 182-183; EX2006 ¶ 63. So-456 explicitly discloses such an extension because, as Petitioner notes, the capture probe

is explicitly “available for enzymatic extension.” Paper 2 at 40; Ex. 1005 ¶ 109; EX2006 ¶ 63.

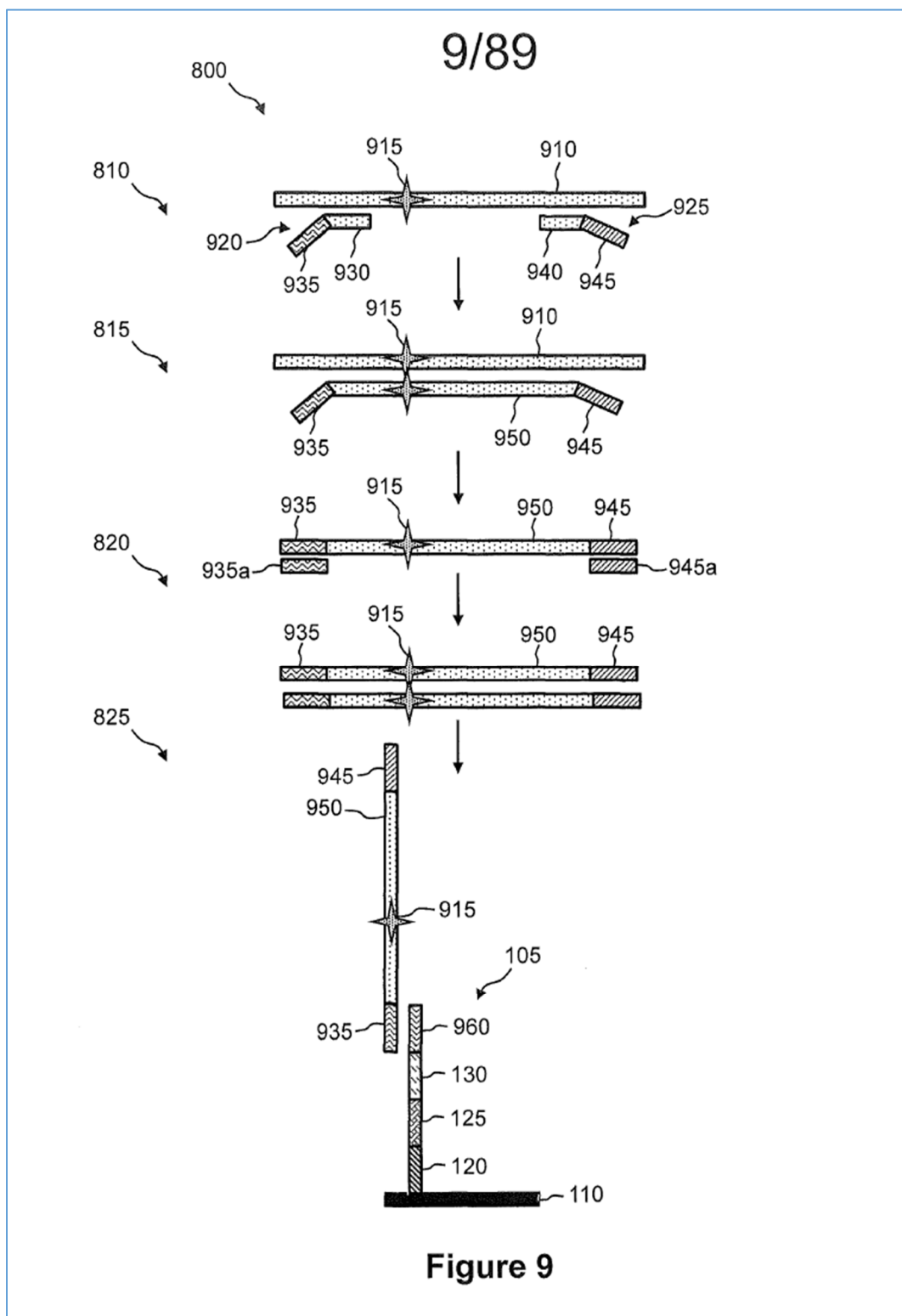
Contrary to these disclosures, Petitioner contends that a “bi-directional” extension is necessarily occurring. Paper 2 at 25-26. Petitioner relies on a version of So-456’s Figure 9 annotated by Petitioner’s expert to demonstrate the “bi-directional” extension. *Id.* Neither Figure 9, nor the accompanying description, support Petitioner’s contention:



EX1005 Fig. 9. As is clear from the unannotated version of Figure 9, no “bi-directional” extension is necessarily occurring. EX2006 ¶ 63. Nowhere in the figure or description is a “bi-directional” extension reaction described. *Id.* Petitioner fails to point to any embodiment in So-456 wherein such a bi-directional

extension takes place. Even if the capture probe in Figure 9 contained a spatial address region, that sequence would not be incorporated by any of the uni-directional embodiments. EX2006 ¶ 63. As Dr. Sherman explains, in Figure 9, the extension reaction would incorporate the target sequence onto the capture probe, but does not necessarily incorporate the capture probe sequence back onto the target strand. *Id.*

In fact, when Figure 9 is looked at as a whole, it is clear that the amplification step Petitioner relies upon has nothing to do with the incorporation step at the end:



EX1005 at Fig. 9. As So-456 describes, step 815 is an “extension/ligation” reaction wherein an amplicon containing a mutation (915) is extended using a gene-specific primer with a universal capture region (935). *Id.* ¶ 182. At step 825, the step annotated by Dr. Spellman, So-456 describes capture but no extension step—the only extension taught is the extension/ligation reaction that occurs two steps earlier at step 815. *Id.*; EX2006 ¶ 63.

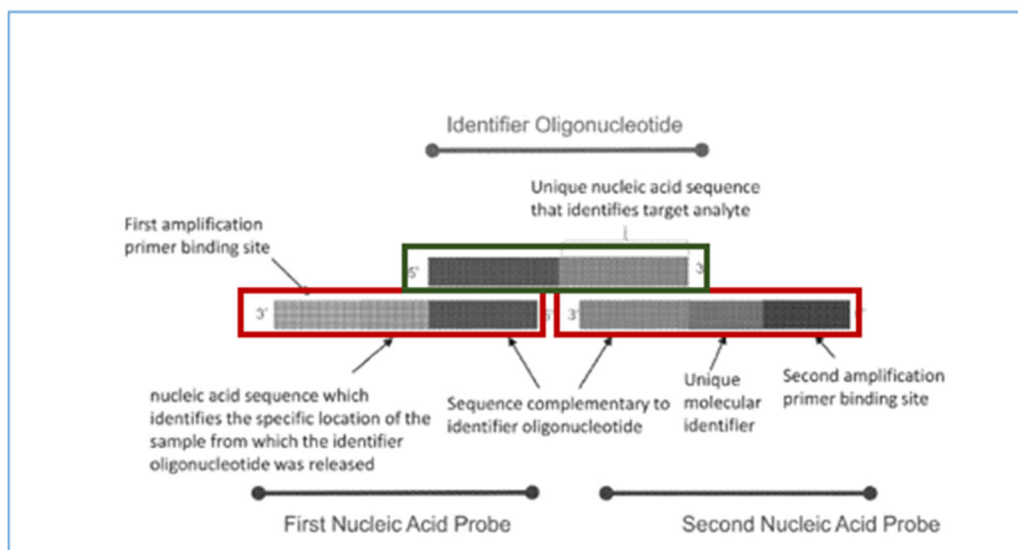
Petitioner also contends, without evidence, that the extension reaction in Figure 9 is necessarily bi-directional because “So-456 did not teach methods for preventing the extension from occurring.” Paper 2 at 25. Such attorney argument is insufficient to show that bi-directional extension must necessarily occur, as required to demonstrate inherency. In fact, Dr. Sherman explains that Petitioner’s premise is incorrect. EX2006 ¶ 64. A skilled artisan would have recognized challenges with bi-directional extension, and the prior art would have needed to teach a method to permit bi-directional extension to occur, *not* a method to stop it from occurring. *Id.* The Board acknowledged Petitioner’s deficient arguments, stating that “Petitioner does not show sufficient evidence of inherently bi-directional extension” and that Petitioner did not show 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.” Paper 14 at 28; EX2006 ¶ 65.

4. So-456 Does Not Disclose Forming Ligated Probes

Claim 16 requires ligating two nucleic acid probes to form a ligated probe:

b) forming ligated probes by ligating each of the 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.

EX1001 Claim 16(b). As the '689 Patent specifies, a first nucleic acid probe and a second nucleic acid probe hybridize to an identifier oligonucleotide *such that the first and the second nucleic acid probes are adjacent and not overlapping*. *Id.* at 25:51-54. Dr. Sherman's annotation of Figure 5 provides a visual representation of the adjacent, non-overlapping probes hybridizing:

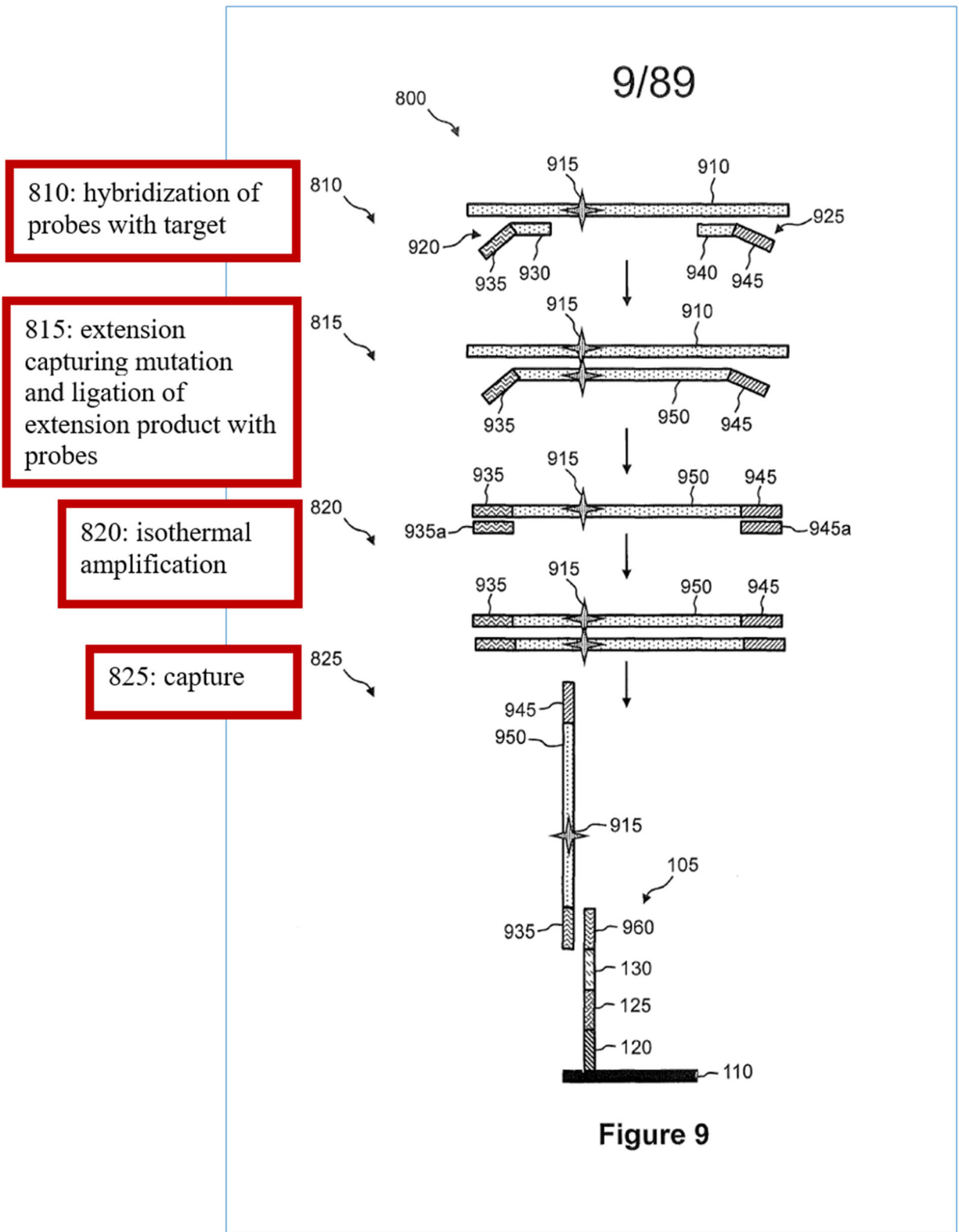


EX1001 Fig. 5; EX2006 ¶¶ 66-67. The two probes are highlighted in red, while an identifier oligonucleotide is highlighted in green. EX2006 ¶ 67. These adjacent

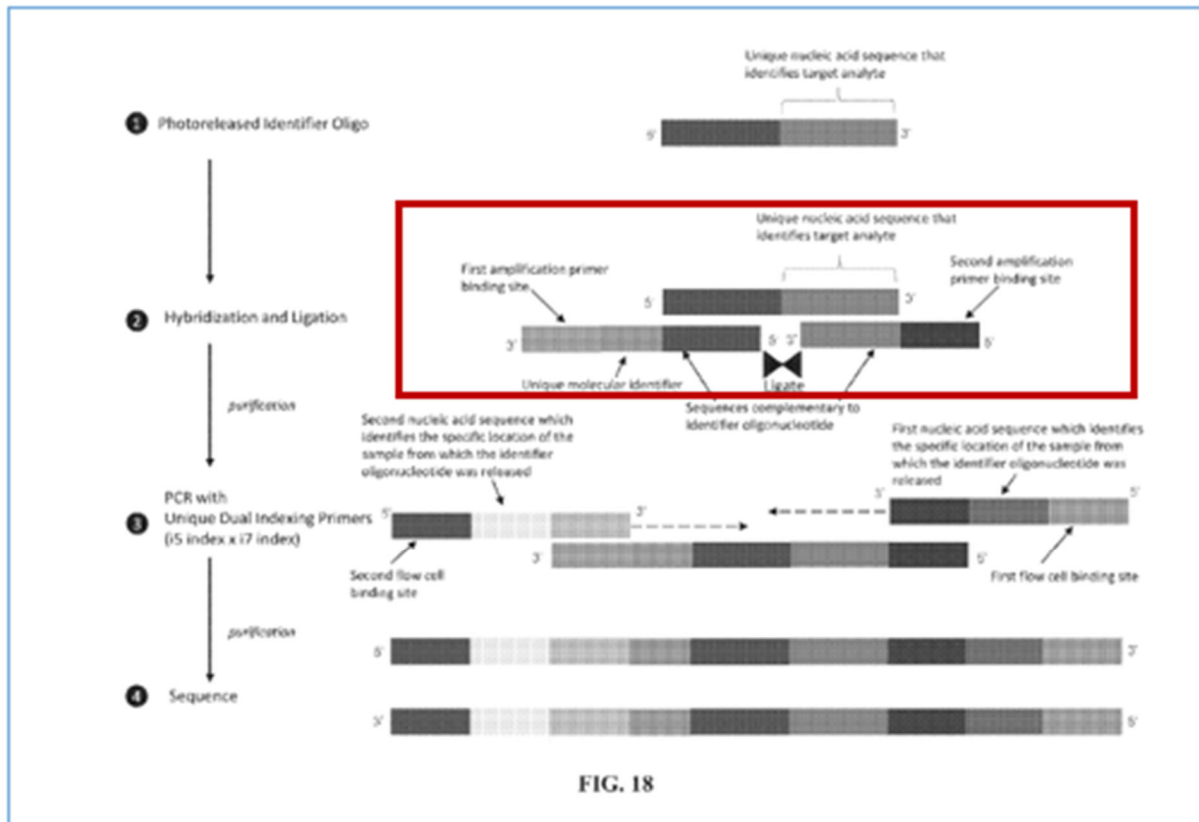
probes may be ligated together by, for example, a “nick repair reaction.” EX1001 at 25:64-65. Based on the disclosures in the ’689 Patent, “ligating probes” refers to ligating adjacent, non-overlapping probes with techniques consistent with the skill in the art, such as a nick repair reaction. EX2006 ¶ 68; *see, e.g.*, EX1001 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); *id.* at 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.

As Petitioner concedes, So-456 discloses two nucleic acid probes that are “not adjacent and not overlapping.” *See* Paper 2 at 19; *see also* EX1005 ¶ 182 (“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.”). Petitioner relies on disclosure of “an extension/ligation reaction” that is “performed in situ between the flanking capture oligonucleotides 920 and 925 across the region of interest,” arguing that this reaction forms the ligated probes as claimed. Paper 2 at 19; EX1005 ¶ 182. So-456, however, does not disclose ligating probes as they are ligated in the ’689 Patent. As Dr. Sherman explains, rather, the “extension/ligation reaction” is a step wherein an extension

captures the mutation of interest between two probes, and then each probe is ligated to the extension product. EX2006 ¶ 69. Dr. Sherman's annotation of Figure 9 in full demonstrates this step:



EX2006 ¶ 70. As Dr. Sherman demonstrates, step 815 features an extension to capture the mutation and ligation of probes to an extension product. *Id.* This contrasts with the '689 Patent's disclosures at, for example, Figure 18:



EX1001 Fig. 18; EX2006 ¶ 70. As Dr. Sherman highlights in step 2 of Figure 18, the ligation reaction occurs directly between the probes. *Id.* PCR then occurs on the ligated probe product. *Id.* 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* Paper 2 at

19. Without explanation, Petitioner's expert simply labels the entire "extension/ligation reaction" as a "ligation." Petitioner, however, cannot generate disclosure through their expert's annotation. Furthermore, to the extent that Petitioner claims that the '689 Patent's disclosure of a "gap extension reaction and a nick repair reaction" is somehow equivalent to So-456's extension/ligation reaction, this is incorrect. As Dr. Sherman explains, the "gap extension reaction" merely exists in the case where the probes are not close enough to each other to successfully ligate. EX2006 ¶¶ 71-72. Unlike So-456's extension/ligation, it is not meant to capture an amplicon to collect meaningful data, and a skilled artisan would not equate the two. *Id.* Accordingly, So-456 does not disclose the ligation limitation.

B. GROUNDS 2 AND 3: CLAIMS 1-30 WOULD NOT HAVE BEEN OBVIOUS OVER SO-456

In Ground 2, Petitioner argues in the alternative that if So-456 does not anticipate the challenged claims, it renders them obvious. Petitioner's argument is focused on the claimed extension steps. Ground 3 uses So-456 as the base reference and relies on Stahl only for additional limitations in claims 9-10 and 24-25. Because So-456, alone, does not render claims 1 and 16 obvious, both Grounds 2 and 3 fail. EX2006 ¶ 73.

1. So-456 Does Not Render The Claimed Extension Steps Obvious

Petitioner relies on many of the same disclosures in its obviousness argument as it does in its anticipation argument, and attempts to fill gaps with unsupported logical leaps from Dr. Spellman's testimony. According to Dr. Spellman, a POSA "would have known that So-456's methods incorporate a spatial barcode in the target nucleic acids by tagging the nucleic acids with a probe containing a spatial barcode," and therefore, it would have been obvious to a skilled artisan to modify the procedures to incorporate them by extension. EX1002 ¶ 220. As Dr. Sherman explains, however, adding a spatial barcode by extension is actually an inventive step that was a nonobvious improvement over the prior art. EX2006 ¶¶ 74-75.

Petitioner's argument is based on the erroneous premise that So-456 discloses bidirectional extension of captured oligonucleotides. As detailed above, So-456 does not disclose bidirectional extension, and there is not even evidence that the capture probe contains a spatial address region. EX2006 ¶ 76. Beginning with this erroneous premise, Petitioner relies on Dr. Spellman's testimony to propose that because So-456 uses sequencing-by-synthesis (SBS) with paired-end sequencing, So-456 *must* suggest the use of an extension reaction to incorporate a spatial barcode. EX1002 ¶ 224. As Dr. Sherman explains, however, Dr. Spellman is incorrect. EX2006 ¶ 77. Rather, all that the need to add SBS primers shows is that two

unidirectional SBS reactions occur. *Id.* ¶ 78. And nothing about the need to add an SBS primer explains why a spatial barcode *must* be added; in fact, the capture probe does not even contain a spatial barcode. *Id.* Even if all of Petitioner’s premises were correct, Petitioner’s argument still does not result in disclosure of an extension reaction that adds a spatial barcode. *Id.*

Furthermore, even if Petitioner and Dr. Spellman could show that all the elements exist in So-456 (which they cannot), Petitioner fails to provide any motivation to modify the methods in So-456. EX2006 ¶ 79. If Petitioner is to be believed, then when the *captured* probe, which is the molecule that features the target sequence and a universal capture sequence ligated together, hybridizes to the *capture probe*, which is the sequence affixed to the array, the bidirectional extension already results in a molecule that has the necessary sequences for SBS. *Id.* ¶¶ 80-82. Therefore, there is no need to modify the method to perform such an extension reaction. *Id.* This is consistent with the Board’s findings in its Decision Granting Institution, wherein the Board found that Petitioner “does not sufficiently show a motivation for the ordinarily skilled artisan to have included a spatial barcode in the capture probes of So-456.” Paper 14 at 31; EX2006 ¶ 83.

C. Chell Does Not Anticipate Claims 1-30

Petitioner's ground 4 is based on the allegation that Chell anticipates the '689 patent claims. Chell, however, was not published until 2021 and is thus not prior art. Petitioner nonetheless argues that the '689 patent's priority application, the '487 application, lacks written description support for the '689 patent claims because it allegedly fails to disclose "collecting whole probes" and "a particular arrangement and usage of primary (analyte-binding) probes." Paper 2 at 53, 55.

Contrary to Petitioner's allegations, the '487 application properly supports the '689 patent claims. As the Federal Circuit recently affirmed, a "specification adequately describes an invention when it 'reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.'" *Allergan USA, Inc. v. MSN Lab'ys Priv. Ltd.*, No. 2024-1061, 2024 WL 3763599, at *9 (Fed. Cir. Aug. 13, 2024) (citations omitted). Further, "the 'hallmark' of written description" is that "the disclosure must be considered as a whole, as the person of ordinary skill in the art would read it, to determine if it *reasonably* conveys possession." *Id.* at *11 (citation omitted) (emphasis in original).

Here, Petitioner contends that two features are not adequately disclosed in the '487 application. It is well established, however, that a "claim will not be

invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language.” *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) (citation omitted). “That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before.” *Id.* During cross-examination, Petitioner’s expert agreed that “a patentee may rely on information that is well-known in the art for purposes of meeting the written description requirement.” EX2007 at 90:2-92:20; EX2050 at 19-21 (citations omitted).

This is particularly relevant here, where the parties agree that a POSA is highly skilled, with a Ph.D. in a relevant field and two years of relevant experience. EX1002 ¶ 24. As Petitioner’s expert, Dr. Spellman, confirmed on cross-examination, a POSA would have a strong understanding of spatial analysis including high-throughput sequencing, oligonucleotide hybridization, barcode tagging, and specific ligation, among other competencies. EX2007 at 46:10-49:20. Given this extensive background knowledge, there can be no question that a POSA would have understood from the specification that the inventors of the ’689 patent possessed the invention as claimed. EX2006 ¶¶ 84-90.

1. Collecting “Whole Probes” Is Disclosed

Petitioner contends that the '487 application “never discloses[s] releasing or collecting *whole* probes,” as encompassed by the claim step of “collecting the...probes, or portions thereof.” Paper 2 at 54. The specification, however, sufficiently discloses using entire probes such that a POSA would have understood “whole probes” to have been envisioned and disclosed by the inventors. EX2006 ¶¶ 88-104.

In the claims, probes are part of a “contacting” step in which a plurality of probes are contacted with a tissue sample and “comprise a target binding domain that binds to the at least one target analyte.” EX1001 Claims 1(a), 16(a). Subsequently, a “collecting” step requires collecting probes that are “bound to the at least one target analyte in a first/second location of the tissue sample under conditions that release the...probes.” *Id.* Claims 1(b)-1(c), 16(c)-16(d).

According to Petitioner, the '487 application “disclosed primary probes [] made up of two separable parts, a target-binding domain...and an identifier oligonucleotide” and that “the identifier oligonucleotide portions...are cleaved and collected.” Paper 2 at 54. Thus, Petitioner contends that the '487 application does not provide support for the full breadth of the claims because it discloses only releasing parts of probes and not entire probes. *Id.*

Despite Petitioner’s contention that “the patent does not describe cleavage as an optional feature” (Paper 2 at 55), nowhere does the ’487 application *require* cleavage to release the probe. EX2006 ¶¶ 92-93. Just the opposite, the specification explicitly describes embodiments of probes with a cleavable linker between the “identifier oligonucleotide” and the “target binding domain” as “a non-limiting example.” *See, e.g.*, EX1009 ¶¶ 106-107, 123-127, 131, 140-145, 159, 176, 180, 184, 200-201, 211, 221, 236, 246, 315-317. The ’487 application further teaches that the cleavage site can be on another sequence when it states that the “constant nucleic acid sequence can also comprise a cleavable moiety.” *Id.* ¶¶ 18, 131; EX2006 ¶ 93.

Consistent with this, in addition to cleavage, the ’487 application teaches other widely used techniques that would release not just a portion of a probe but an entire probe. EX2006 ¶ 94. One such disclosed technique is separating the probe from the target analyte through denaturation. As the ’487 application teaches, “[s]uitable denaturing conditions will be apparent to the skilled reader with reference to standard molecular biology protocols.” EX1009 ¶ 285. And, during cross-examination, Petitioner’s expert agreed that “denaturation is well known to a POSA.” EX2007 at 114:6-7. In addition to cleaving off a portion of the probe, a

POSA would have known that the entire probe can be released from the target analyte through denaturation. EX2006 ¶ 94.

And, in fact, the '487 application discloses specific examples of entire probes being released from target analytes through denaturation. *Id.* ¶¶ 95-100. For example, this is demonstrated in patent application No. 14/946,386, an application by a co-inventor that is incorporated by reference. EX1009 ¶¶ 64, 216, 227 (“US2014946386...is incorporated herein by reference in its entirety.”). There, the specification discloses entire probes that hybridize and de-hybridize from a target nucleic acid to determine its sequence. *See* EX2008 ¶ 10 (“hybridizing at least one sequencing probe...to an target nucleic acid”); *id.* ¶ 12 (“de-hybridizing each sequencing probe of the first population from the nucleic acid” and “removing each de-hybridized sequencing probe of the first population”); *id.* Figs. 8A-8E; EX2006 ¶ 97.

The specification of the '386 Application further teaches that probes can reversibly hybridize to their targets and that de-hybridization can be controlled by the “level of chaotropic agent, temperature, salt concentration, pH, and hydrodynamic force.” EX2008 ¶ 11; EX2006 ¶ 98. Probes can even be designed “to control the likelihood of hybridization and/or de-hybridization and the rates at which these occur.” EX2008 ¶ 86. A working example of hybridizing and de-

hybridizing entire probes is included. *Id.* ¶¶ 174-194. A POSA would have understood that these probes are part of the '487 application's disclosure, since the '487 application teaches that "[a]ny probe or set of probes described herein may be used in methods and kits of the present disclosure." EX1009 ¶ 259; EX2006 ¶ 99-100. As Dr. Sherman explains, a POSA would have understood from this broad disclosure that "whole probes" can be released via denaturation by de-hybridizing entire probes from their target. EX2006 ¶ 100. When asked whether a POSA would know "how to denature a probe that's attached to a target of interest," Petitioner's expert responded that "denaturation is well known to a POSA." EX2007 at 113:25-114:7.

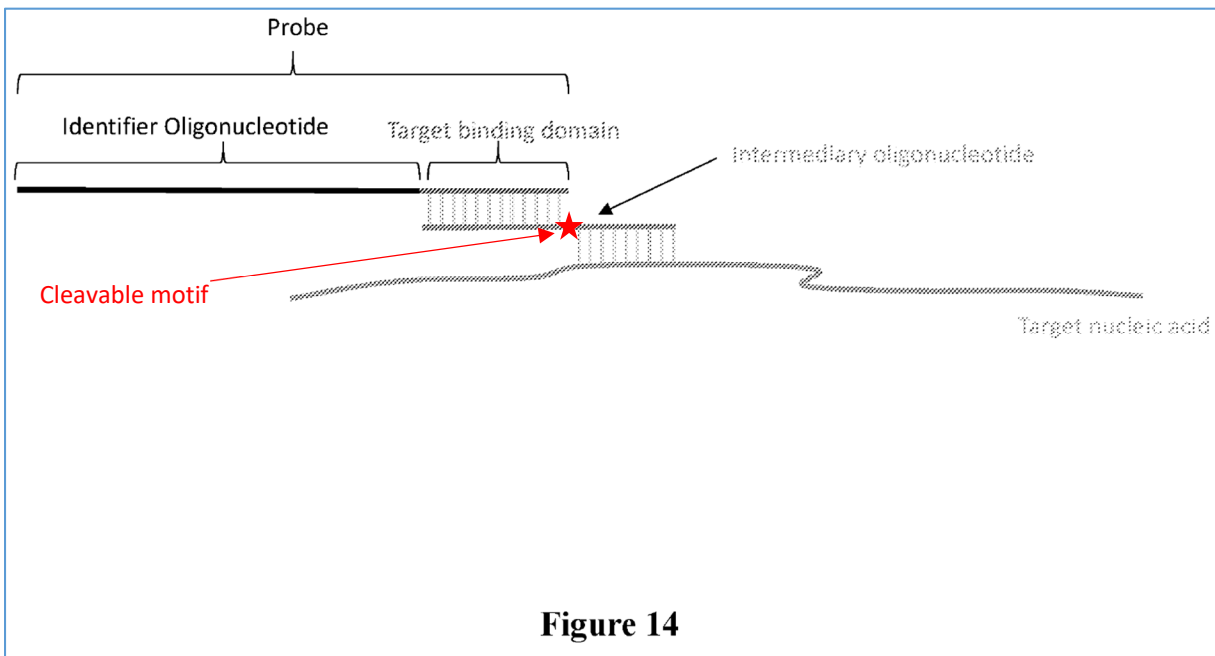
Furthermore, the '487 application clearly discloses uncleaved "whole probes" when it teaches "performing a negative purification of the *intact probe molecule*." EX1009 ¶ 252. Since this purification of "intact probe molecule" takes place "after collection of eluate from a region of interest" (*id.*), a POSA would have understood that the probes were uncleaved, because if cleavage took place, both bound and unbound probes would have been affected, such that there would not be "intact" unbound probes to be purified. EX2006 ¶ 101.

As additional support for the release of "whole probes," the '487 application never states that the "target-binding domain" and "identifier oligonucleotide"

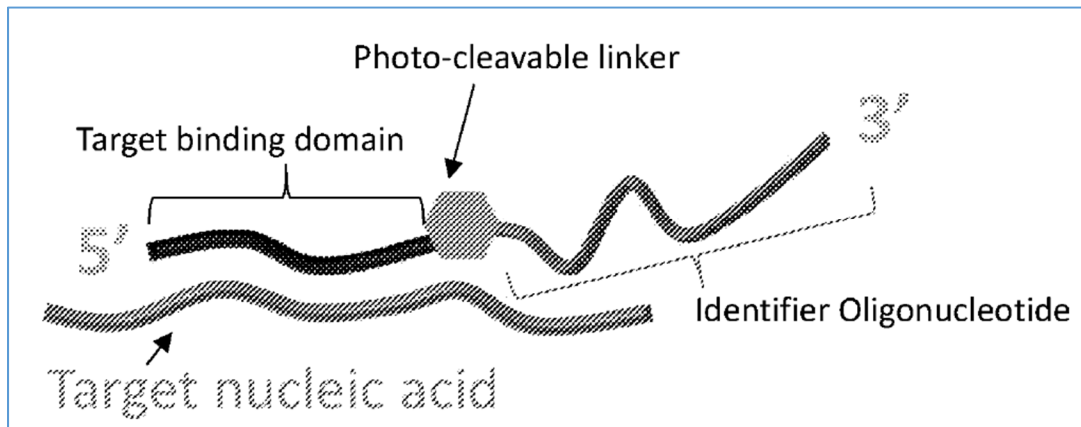
portions of a probe cannot overlap or even be the same sequence. The specification describes both portions in functional terms: the “target-binding domain” is a sequence that “can directly or indirectly hybridize to a target nucleic acid of interest” and an “identifier oligonucleotide” is a sequence “which identifies the target analyte bound to the target binding domain.” EX1009 ¶¶ 106, 126, 144, 158, 183, 199. Nothing forecloses the same sequence from serving both functions. Accordingly, a POSA would have understood that a probe can bind to a target analyte and subsequently be completely released via de-hybridization. EX2006 ¶ 102.

As if the foregoing were not enough, the ’487 application includes yet additional disclosures of “whole probes” in connection with its teaching of indirect hybridization. The specification teaches that “the probes of the present disclosure can indirectly hybridize to a target nucleic acid present in a sample (via an intermediary oligonucleotide).” EX1009 ¶ 233; *see also id.* ¶¶ 106, 310 (disclosing probes that indirectly hybridize to a target analyte). It further teaches that “the intermediary oligonucleotide is a probe, as defined herein, since it comprises a nucleic acid backbone and is capable of binding a target nucleic acid.” *Id.* ¶ 233. Being a “probe of the present disclosure,” an intermediary oligonucleotide “can include a region which permits the release of an identifier oligonucleotide following the application of a suitable force,” where “the region is

a cleavable motif.” *Id.* ¶ 246. As Dr. Sherman explains, a POSA would have understood that the “intermediary oligonucleotide” can include a “cleavable motif” so that the entire probe comprising the “target binding domain” and “identifier oligonucleotide” can be released, as depicted in this annotated figure, wherein the star shows the location where a POSA would have understood the specification contemplates the use of a “cleavable motif”:



EX1009 Fig. 14 (annotated); EX2006 ¶ 103. This is consistent with disclosures of a probe with a cleavable linker bound to a target analyte:



EX1009 Fig. 13; EX2006 ¶ 103.

For at least the above reasons, the '487 application “reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter”—the release of “whole probes” from target analytes—“as of the filing date.” *Allergan*, 2024 WL 3763599, at *9; EX2006 ¶ 104.

2. “On-Analyte Ligation” Is Disclosed

Petitioner’s remaining written description argument is that “on-analyte ligation” is not disclosed. Paper 2 at 55-57. Petitioner’s argument is based on two allegations: (1) probes in the '487 application do not hybridize to a target analyte (“on-analyte”) and (2) ligation in the '487 application does not occur while hybridized (“ligation”). *Id.* As documented below, however, these theories are premised on the legally erroneous theory that a specification must enable and describe a product accused of infringing. And, in any event, the '487 application

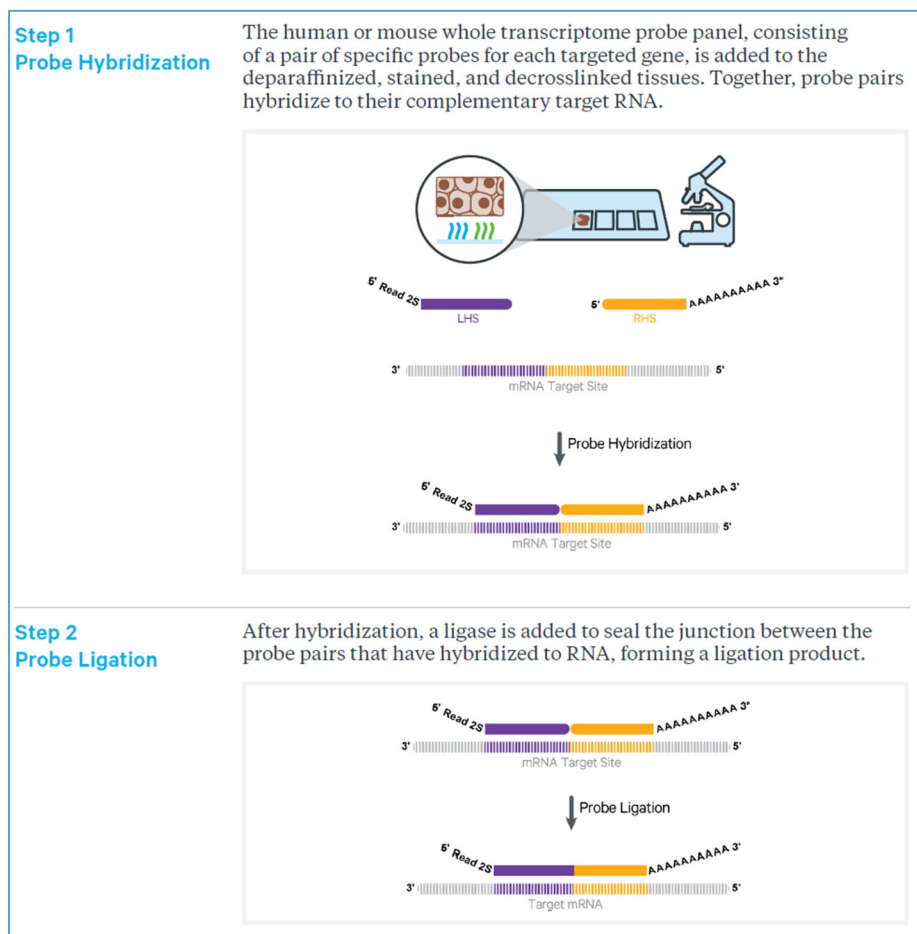
fully discloses both of the concepts that Petitioner contends are absent. EX2006 ¶¶ 105-122.

a. Petitioner's Product Need Not Be Described

At the outset, Petitioner's argument focuses on one set of embodiments in the '487 application, rather than the complete disclosure, and attempts to draw a distinction with Petitioner's own product, which practices the '689 patent claims. EX1020. Contrary to law, Petitioner introduces a series of terms not found in the '487 application—primary, secondary, on-analyte, off-analyte—that describe

Petitioner's product and inappropriately uses them to allegedly show the '487 application's defect. EX2006 ¶ 106.

For example, Petitioner's product involves “probe pairs [that] hybridize to their complementary RNA” and the addition of “a ligase...to seal the junction between the probe pairs that have hybridized to RNA, forming a ligation product”:



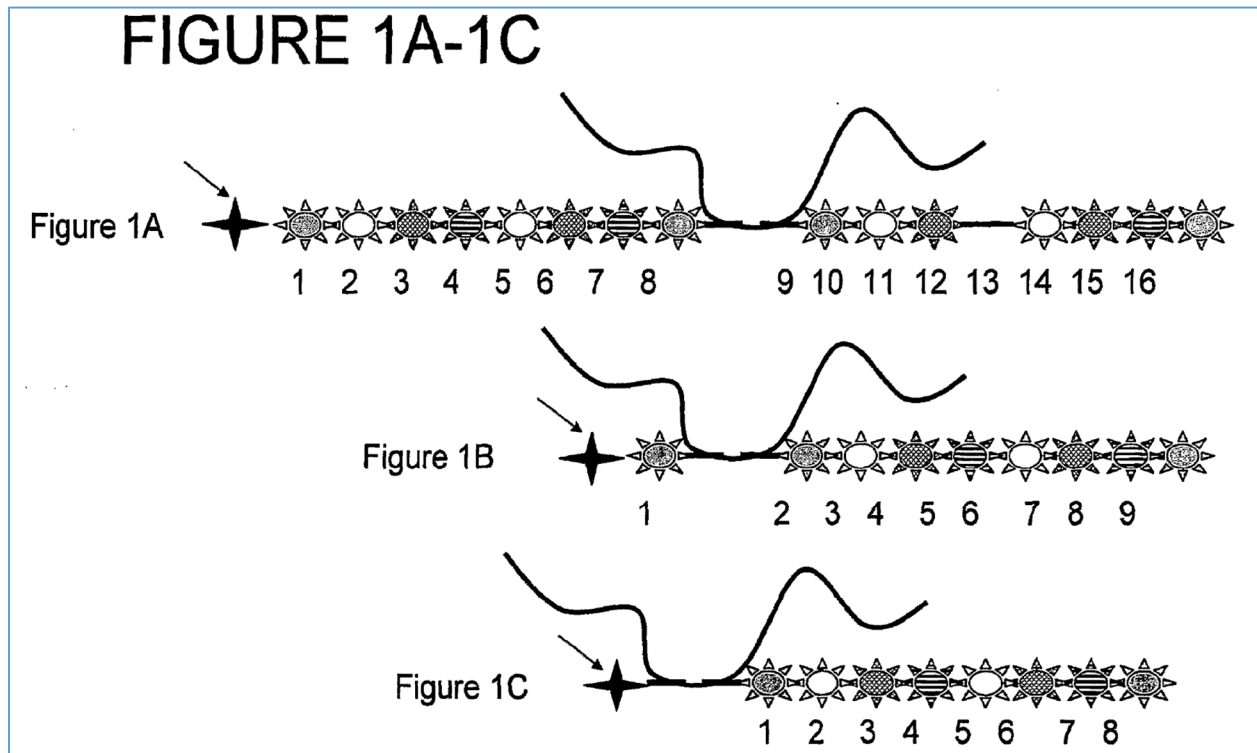
Id. at 83; EX2006 ¶ 107. There is no need, however, for the '487 application to describe this exact product, as it has long been held that a patent “need not describe and enable the accused device.” *Microchip Tech. Inc. v. Aptiv Servs. US LLC.*, No.

17-CV-01194, 2020 WL 4435510, at *6 (D. Del. July 31, 2020) (citing *Epistar Corp. v. Int’l Trade Comm’n*, 566 F.3d 1321, 1336 (Fed. Cir. 2009)). That is because an “applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention.” *Epistar*, 566 F.3d at 1336. Petitioner’s attempt to measure the adequacy of written description based on whether the ’487 specification discloses Petitioner’s accused product is unsupported in law and is reason enough to reject its written description arguments.

b. The ’487 Application Discloses Probes That Bind To The Target

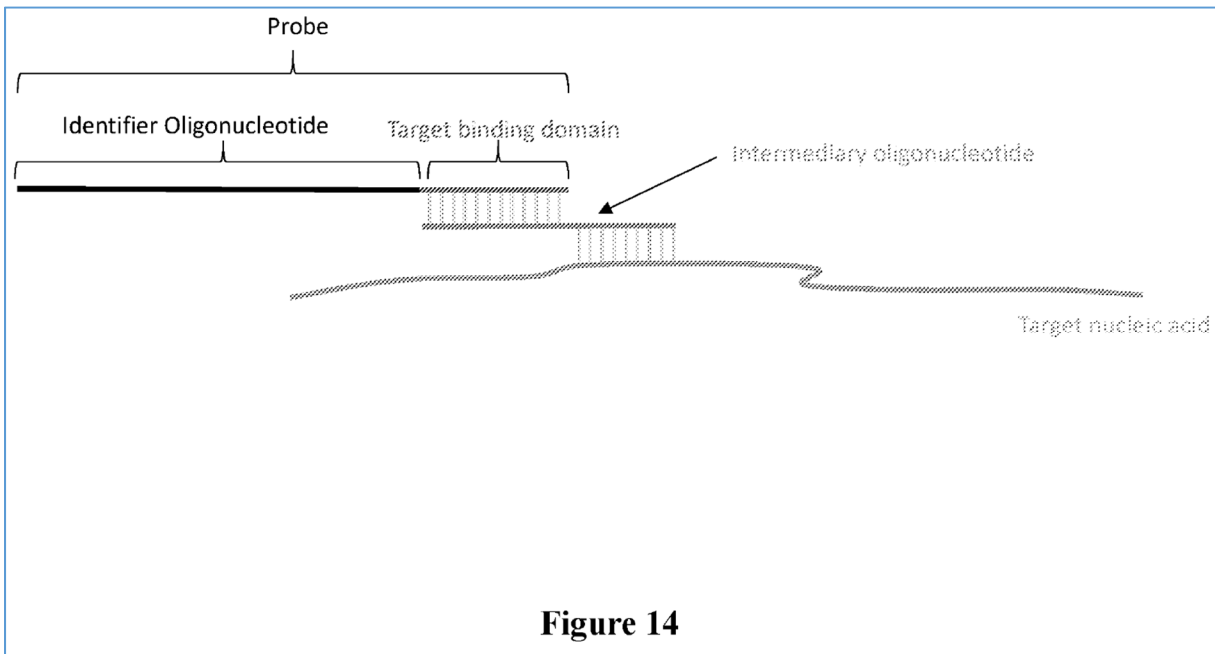
Petitioner’s first alleged defect in the written description of the ’487 application is that it allegedly does not disclose hybridizing probe pairs directly to a target analyte. EX2006 ¶¶ 108-113. Petitioner concedes, however, that the “priority applications describe...*in situ* hybridization of cleavable ‘probes’ comprising a target-binding domain.” Paper 2 at 55; EX2006 ¶ 109.

In addition, the ’487 application also discloses probe pairs that hybridize to a target analyte. For example, patent application publication no. 2010/0015607, incorporated by reference, teaches a “probe pair” comprising a first probe with “a first target-specific sequence attached to the first molecule” and a second probe with a “second target-specific sequence.” EX2009 ¶ 13. As depicted below, the reference teaches two probes that hybridize to a target analyte:



Id. Figs. 1A-1C. A POSA would have understood these probe pairs to be part of the '487 application, which specifically incorporates the reference for “[p]robes and methods for binding and identifying a target nucleic acid.” EX1009 ¶ 232; EX2006 ¶¶ 110-111.

In addition to the foregoing, the '487 application teaches hybridization to the target using an indirect target binding domain. Specifically, the application discloses that “the probes of the present disclosure can indirectly hybridize to a target nucleic acid present in a sample.” EX1009 ¶ 233. This concept is depicted in Figure 14, which shows a probe indirectly bound to a target analyte via a “target binding domain”:



Id. Fig. 14. Accordingly, a POSA would have understood that probes, including the claimed “nucleic acid probes,” can *indirectly* bind to target analytes. EX2006 ¶ 112. A POSA would have understood that such indirectly binding probes are “bound to each of identical molecules from the at least one target analyte,” as claimed. *Id.*

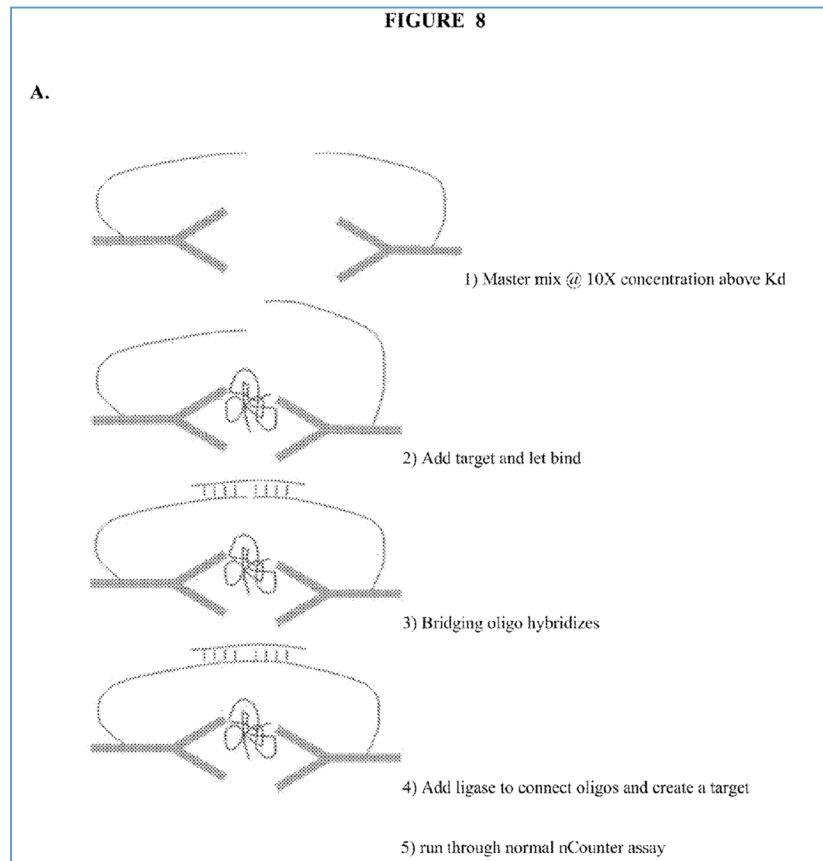
Thus, there is extensive disclosure in the '487 application teaching hybridizing probes to the target via several different mechanisms and approaches. To the extent Petitioner contends otherwise, there is still no written description defect. This is because such techniques for binding probes to targets were so basic and fundamental they would have been well within the background knowledge of a POSA, such that the '487 application would not need to provide more detailed

description. *Id.* ¶ 113. Despite Petitioner’s expert stating that a POSA could likely practice the ’689 patent claims due to their high skill level (EX2007 at 72:15-73:3, 92:23-93:3), Petitioner presents no argument why a POSA would be unable to utilize probes that hybridize to a target.

c. The ’487 Application Discloses Ligation Of Probes

The ’487 application also discloses ligating probe pairs. EX2006 ¶¶ 114-122. For example, the application discloses “performing nick repair such that the hybridized first and second nucleic acid probes are ligated together.” EX1009 ¶ 24. As discussed in the prior section, probe pairs can indirectly hybridize to a target analyte, as disclosed by the application, prior to ligation. EX2006 ¶ 115. To the extent Petitioner argues that the ligation must occur while the probe pair is hybridized to the target analyte, a POSA would have understood that this is disclosed as well, since the specification does not require disclosed steps to take place in order. EX2006 ¶ 116.

The ’487 application discloses ligating two nucleic acids both bound to a third nucleic acid. For example, patent application publication no. 2011/0086774, incorporated by reference, discloses a first and second oligonucleotide that are brought in proximity, hybridized to a “bridging oligo,” and ligated together by a ligase. EX2010 ¶ 37. This process is depicted below:

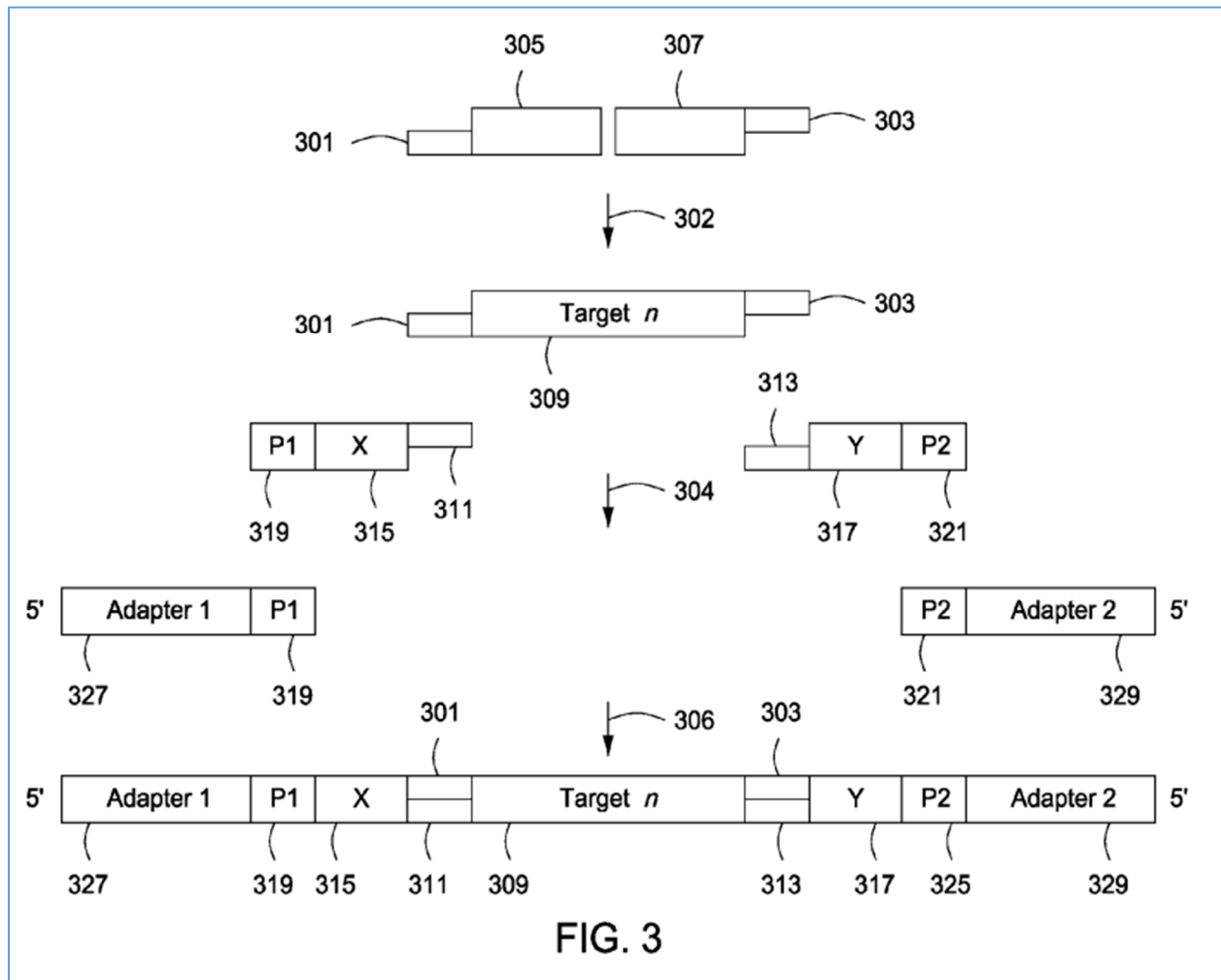


Id. Fig. 8A. A POSA would have understood this to disclose designing two oligonucleotides that can be ligated while hybridized to a third and understood that this is analogous to the allegedly missing feature. EX2006 ¶ 117.

To the extent Petitioner argues that the '487 application's disclosure is somehow deficient, the disclosure must be understood in the context of a POSA's background knowledge. Here, Petitioner's expert specifically states that ligation is a "simple skill," such that "a person of ordinary skill in the art would be familiar with ligation as a broad concept, extremely broad, and how and when it can be utilized effectively." EX2007 at 49:6-9, 76:15. Petitioner's expert further

emphasizes that a “POSA has a set of competencies, things they know how to do -- ligation being a common one, for example.” *Id.* at 75:6-8. In other words, ligation of probes is yet another skill that was fundamental and well-known in the art, such that a POSA would not even need detailed teaching regarding this technique in the ’487 application. EX2006 ¶¶ 118-120.

The longstanding and fundamental nature of ligation of probes is clear from Petitioner’s own patents. The ’689 patent discloses Petitioner’s patent publication No. 2011/0245111, a prior art reference that Petitioner acquired from a company called Prognosys. EX2011 at 208. There, Petitioner’s patent application specifically describes hybridizing two probes to a target analyte and ligating the probes, analogous to the claimed feature:



EX2012 Fig. 3. As the 2011 reference describes, *eight years* prior to the '487 application's filing, "two oligonucleotide probes are provided" that each "comprises a target-specific region...seen at 305 and 307" and "are allowed to hybridize to a target nucleic acid (not shown)...and ligated...to form an extended probe." *Id.* ¶ 54. Thus, ligating two probes hybridized to a target analyte is well known and would have been part of a POSA's background knowledge. EX2006 ¶ 121.

For at least the above reasons, the '487 application “reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter”—ligating probe pairs hybridized to a target analyte—“as of the filing date.” *Allergan*, 2024 WL 3763599, at *9. EX2006 ¶ 122.

3. Petitioner’s Arguments Contravene Federal Circuit Law

As documented above, the '487 application includes more than sufficient disclosure of both binding and ligating probes. Beyond this, these techniques were undisputedly routine techniques that were within the wheelhouse of the POSA. Nevertheless, Petitioner contends that the claims of the '689 patent are too broad to be supported by the '487 application. Instructive on this issue is the Federal Circuit’s recent decision in *Allergan*, which shows that Petitioner’s contention regarding written description are without merit.

In *Allergan*, the claims were directed to a formulation without a component, a glidant, which was allegedly required. Thus, “the issue is whether the inventors had possession of a formulation that lacked a component that is *not* claimed, or only optional.” 2024 WL 3763599, at *9. The Court found that claims that did not include a limitation requiring a glidant was supported by modest disclosure. Even though “the specification does largely focus on more detailed formulations that include a glidant,” the “very fact that a glidant is not necessarily present in every

embodiment indicates that it is optional, regardless whether the inventors expressly described it as ‘optional.’” *Id.* at *11. Moreover, “without some basis in the specification that the invention would be understood to require a glidant, expert testimony cannot be used to fill that gap.” *Id.* at *12. “Reliance on such testimony, untethered to the inventors’ own description of the invention, would improperly take the written description inquiry outside the four corners of the specification.” *Id.*

Here, for instance, Petitioner’s argument is essentially that the ’689 patent claims are overbroad because the ’487 application discloses “off-analyte ligation” and not “on-analyte ligation.” As discussed above, however, even though the “specification does largely focus on more detailed [embodiments] that include” what Petitioners labels “off-analyte ligation” (*id.* at *11), there is support for “on-analyte ligation”—particularly in view of a POSA’s knowledge, which Petitioner does not dispute. Moreover, Petitioner provides no basis other than expert testimony as to why “on-analyte ligation” is allegedly required, which “improperly take[s] the written description inquiry outside the four corners of the specification.” *Id.* at *12. Accordingly, whether ligation occurs “on-analyte” is optional. As the Federal Circuit found in *Allergan*, the Board should conclude here that there is adequate written description.

V. CONCLUSION

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

Dated: August 26, 2024

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 10,067 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: August 26, 2024

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PATENT OWNER'S RESPONSE TO PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 11,377,689 and EXHIBITS 2006-2015, 2050-2052** were served on August 26, 2024, via email pursuant to 37 C.F.R. § 42.6(e) to counsel for Petitioner at the addresses below:

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